Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

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Kendra Stewart, R.Ph., Pharm.D.
Supervisor, Orange Book Staff
Division of Legal and Regulatory Support
Office of Generic Drug Policy
Building WO-75, Room 1684
10903 New Hampshire Avenue
Silver Spring MD 20993-0002

By Electronic Mail

Re: Exclusivity decision for Prepopik® on remand
NDA 202535[1]

Dear Ms. Stewart:

On behalf of Ferring Pharmaceuticals Inc. (Ferring), we are writing in response to your April 5, 2017 letter requesting scientific and legal arguments on the eligibility of Prepopik (sodium picosulfate; magnesium oxide; citric acid) to be awarded 5-year new chemical entity (NCE) exclusivity.

We note at the outset that this request by the Food and Drug Administration (FDA) is being made following the September 9, 2016 Memorandum Opinion of the U.S. District Court for the District of Columbia in *Ferring Pharms, Inc. v. Burwell*, Case No. 15-00802 (D.D.C. Sept. 9, 2016). In that decision, the District Court held that FDA's denial of NCE exclusivity for Prepopik was arbitrary and capricious. Accordingly, the court remanded the case to FDA "for further proceedings not inconsistent with this opinion."[2] FDA voluntarily dismissed its appeal of that decision on March 17, 2017. An essential premise of the *Ferring Pharms, Inc. v. Burwell* case was that Prepopik includes at least one drug substance (sodium picosulfate) that contains an active moiety (picosulfate) that qualifies as an NCE and is eligible to receive NCE exclusivity. Throughout the litigation, FDA (represented by the Department of Justice) accepted that

[1] Ferring hereby designates this letter and all attachments as confidential commercial and/or trade secret information subject to, among other provisions of law, 21 CFR Part 20.

[2] Memorandum Opinion, *Ferring Pharms, Inc. v. Burwell*, Case No. 15-00802 (D.D.C. Sept. 9, 2016) at 23.

essential premise. Indeed, the government stated repeatedly in the litigation that picosulfate is a new active moiety that has not previously been approved by the agency. *See infra.*

In your April 5 letter, FDA now appears to claim that based on "unusual circumstances" and "further review," the agency may need to reverse course and find that picosulfate is ***not*** a new active moiety and, therefore, that Prepopik is ***not*** eligible for NCE exclusivity. As the letter states:

> it appears that bis-(p-hydroxyphenyl)-pyridyl-2-methane (BPHM, CAS: 603-41-8, UNII: R09078E41Y), the active moiety of sodium picosulfate (CAS: 10040-45-6, UNII: VW106606Y8), also seems to be the active moiety in bisacodyl [(4,4'-diacetoxydiphenyl(2-pyridyl)methane), CAS: 603-50-9, UNII: 10X0709Y6I.[3]

The letter, however, contains no substantive explanation as to how or why the agency – after nearly eight years of experience with the product – is poised to reverse a determination it made and acted on multiple times, in multiple settings, regarding the essential chemistry of picosulfate.

The April 5 letter is an abrupt and unexplained departure from the previous interpretation of the statutory and regulatory provisions as they apply to Prepopik. Not once in the nearly eight years in which FDA has been involved with the product – including the review and approval of Prepopik, an extensive citizen petition process, and litigation over the exclusivity of the product – has the agency identified picosulfate as anything but an active moiety. Now, with no explanation, the agency appears to want to take the position that the covalently bound sulfur-based appendages in sodium picosulfate could be considered "esters."[4]

The time for a new interpretation of the definition of the term "ester," or a new analysis of the chemistry of picosulfate, has long passed. Far too many regulatory and litigation decisions have been based on the agency's original and oft-repeated determination that picosulfate is a novel active moiety, rather than an ester of a previously approved active moiety. Moreover, the agency has provided no new information that would support its apparent change in interpretation, and therefore Ferring lacks any meaningful opportunity to comment upon or respond to the agency's basis for its change in position. If FDA intends to change its interpretation of the term "ester," particularly in this case, the agency must follow appropriate administrative procedures. In addition, whatever interpretation the agency elects to propose in the future, FDA cannot apply it to deny NCE exclusivity to Prepopik, nearly five years after its approval. As detailed in this letter, and as the agency is well aware, Ferring has relied extensively on FDA's previous interpretation that "picosulfate" is not an ester.

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[3] Letter from K. Stewart, R.Ph., Pharm.D., FDA to E. Thygesen, Ferring Pharmaceuticals (Apr. 5, 2017) at 2.

[4] *See* 21 USC 355(j)(5)(F)(ii); 21 CFR 314.108(b)(2); 21 CFR 314.108(a).

Finally, there is good reason why the agency consistently determined over the long history of the development and review of Prepopik that picosulfate is the relevant active moiety. The hallmark of an ester in the FDA-regulatory context is twofold: the presence of a carbon atom and the cleaving of the ester by esterases. It has been in plain view since the time Ferring first presented sodium picosulfate to the agency that the covalently bound appendages incorporated into the active moiety do not contain a carbon atom. Indeed, unlike a carbon-based ester, the appendages in picosulfate contain two double-bonded oxygens, resulting in an energy level and bond strength quite distinct from that of the carbon-based ester in bisacodyl. This leads to the second point: the picosulfate appendages are not cleaved by endogenous esterases. The bond strength is non-ester-like and, thus, the molecule does not behave like an ester. Thus, it is not surprising that FDA has consistently identified picosulfate as a novel active moiety. The agency officials who reviewed the drug, had they taken even a cursory look, would have immediately recognized that picosulfate, lacking a central carbon atom in the portions of the molecule that FDA has removed to arrive at the alleged active moiety, is not an ester under the agency's drug classification and exclusivity framework.

For these reasons, we ask that you finalize the award of NCE exclusivity, as contemplated by the District Court's decision. We also respectfully request that you promptly provide us with copies of any other submissions received by the agency regarding the exclusivity award for Prepopik and permit us an opportunity to timely respond, before taking any action that does not result in an award of NCE exclusivity to Prepopik.

I. FDA has Consistently Determined that the Sulfur-Based Appendages in Sodium Picosulfate are Not Esters, but an Integral Part of the Active Moiety Picosulfate

Throughout the development and review of Prepopik, FDA repeatedly concluded that the active moiety of sodium picosulfate is "picosulfate," an active moiety that had not previously been approved in a new drug application (NDA) prior to Ferring NDA 202535. This determination reflects the considered review of the agency, not merely an isolated remark from a single reviewer. In fact, for nearly eight years, every agency component that reviewed the issue – the review division, the Director for the Center for Drug Evaluation and Research, the Office of the Chief Counsel – concluded that sodium picosulfate contained a novel active moiety, picosulfate, notwithstanding that picosulfate includes sulfur-based functional groups.

This was the agency's carefully considered opinion well before the exclusivity determination for Prepopik was at issue. As early as 2009, before Ferring had even submitted its NDA, the review division repeatedly described Ferring's drug product as a "new molecular entity" (NME).[5] An NME is "an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Federal Food, Drug, and

[5] PIND 101,738, Memorandum of Meeting Minutes (May 13, 2009) at 5 (describing the agency's heightened data requirements to support the submission and approval of a new molecular entity).

Cosmetic Act or has been previously marketed as a drug in the United States."[6] Having concluded – based on multiple opportunities to analyze the chemistry of sodium picosulfate – that picosulfate is a novel active moiety, the agency made all of its regulatory decisions consistent with that conclusion. For example, the review division asked Ferring to provide additional data necessary to characterize Prepopik's novel active moiety.[7]

When Ferring submitted its NDA for Prepopik, FDA again determined that picosulfate was a novel active moiety. Thus, in late 2011, FDA classified the Prepopik NDA as "Type 1 – New Molecular Entity." As described in MAPP 5018.2, "FDA tentatively assigns an NDA classification code by the filing date for a new application and reassesses the code at the time of approval."[8] MAPP 5018.2 articulates clear procedures to ensure that the NDA classification is the result of careful and deliberate agency decision-making. To that end, the review division requests a determination of the appropriate classification code from FDA's Quality Assessment Team at the time of NDA submission and a confirmation of the classification code at the time of approval.[9] In turn, the Quality Assessment Team not only determines the NDA classification code, but it must "document the final classification in the administrative record for the NDA."[10] Consistent with these procedures, FDA confirmed Prepopik's NME classification in the public Drugs@FDA database following approval of NDA 202535 in July 2012. Prepopik remains listed with this NME classification today.[11]

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[6] *See* Drugs@FDA Glossary.

[7] E-mail from M. Scherer, FDA, to R. Hargreaves, Ferring, regarding IND 101738 (PicoPrep) teleconference follow-up (Mar. 19, 2010) ("As we discussed during yesterday's teleconference, your PicoPrep product, containing sodium picosulfate, is a new molecular entity (NME) for the U.S. As such, an extensive safety monitoring program is warranted."); IND 101738, Pre-NDA Meeting Minutes (Apr. 19, 2011) at 4 ("Since picosulfate is an NME, the ADME characteristics of this active ingredient in humans will need to be characterized.").

[8] NDA Classification Codes, Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5018.2 (Nov. 4, 2015) at 2. Although MAPP 5018.2 was not in effect at the time of Prepopik's review, the substantive information and procedural mechanisms described in MAPP 5018.2 are consistent with earlier iterations of this document that were in effect at the time. *See, e.g.*, Draft MAPP 7500.3, Drug and Application Classification (Eff. Dec. 2, 2009).

[9] MAPP 5018.2 at 7.

[10] *Id.*

[11] FDA historically distinguished between the designation of a product as an NME for review purposes (an active moiety not previously approved) and an NCE for exclusivity purposes (an active ingredient containing no previously approved active moiety). *See id.* at 2 n.2. However, in light of the October 2014 final guidance regarding exclusivity for certain fixed-combination products and the District Court opinion in *Ferring*, there is no longer any principled distinction between the two determinations. Except for rare cases not applicable here (such as products that contain multiple active moieties in a single active ingredient), all drug products that have a novel active moiety for NME purposes also qualify for NCE

Among other things, Congress has directed FDA to provide additional review or administrative process to NME drug products, generally over the concern that FDA must carefully consider the safety of a novel active moiety. Consistent with these goals and statutory directives, FDA made several key regulatory decisions – which would have been unnecessary or improper – based on the agency's determination that picosulfate was a novel active moiety. First, the approval letter for Prepopik was signed at the office level rather than at the division level.[12] Second, the Prepopik approval letter explains why the agency did not refer Prepopik to an advisory committee meeting.[13] Finally, following approval of Prepopik in July 2012, FDA included Prepopik in its list of NME approvals for 2012,[14] where the agency publicly takes credit for approving novel active chemical compounds. Each of these requirements applies only to drug products (like Prepopik) that contain a novel active moiety (like picosulfate). Thus, at a time when the exclusivity award for Prepopik was not at issue, FDA never wavered from its determination that the sulfur-based functional groups in picosulfate are part of the active moiety, picosulfate.

Even as FDA considered whether Prepopik was eligible for NCE exclusivity, the agency continued to consider picosulfate to be the active moiety in sodium picosulfate. On July 13, 2012, FDA completed the Exclusivity Summary for NDA 202535. In response to a question seeking to identify all previously approved active moieties in Prepopik, FDA identified several NDAs containing the same active moieties as in magnesium oxide and citric acid.[15] However,

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exclusivity. As a result, FDA must evaluate Prepopik's eligibility for NCE exclusivity using the same analysis that led the agency to conclude that picosulfate is an NME for purposes of review and approval.

[12] Approval Letter, NDA 202535 (July 16, 2012) at 6-7 (signed by Victoria Kusiak, MD, Deputy Director, Office of Drug Evaluation III). *See* 2 FDA Staff Manual Guides 1410.104(I)(C) (granting division directors and deputy directors authority to approve new drug applications other than those that contain "new molecular entities").

[13] *See* 21 USC 355(s) ("[p]rior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved" in an NDA or biologics license application (BLA) [*i.e.*, an NME], FDA must either refer the drug to an FDA advisory committee for review prior to approval or state in the approval letter its reasons for not doing so).

[14] Novel Drug Approvals for 2012, *available at* https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm336115.htm.

[15] NDA 202535, Exclusivity Summary at II.2. (July 13, 2012). The Exclusivity Summary directs the review division to identify drug products containing any previously approved active moieties in a fixed-combination drug product:

> If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

the agency did not identify any previously approved NDA containing picosulfate or any other component of sodium picosulfate.[16]

The agency's interpretation remained consistent even after Ferring and two other sponsors petitioned the agency requesting NCE exclusivity for fixed-combination products containing novel active moieties in combination with previously approved active moieties. Indeed, after considering Ferring's petition for over a year, FDA expressly recognized in its petition response that "[t]he new active moiety in Prepopik, picosulfate, a stimulant laxative, had not been previously approved in any NDA prior to the approval of Prepopik."[17] In response to a petition for reconsideration from Ferring, FDA reiterated its position that Prepopik contained a novel active moiety, picosulfate.[18] That is, after more than twenty months reviewing citizen petitions regarding NCE exclusivity for Prepopik – and more than two years after Prepopik's approval – FDA continued to conclude that picosulfate is ***not*** an ester.[19]

Finally, FDA (through the Department of Justice) maintained its interpretation that picosulfate is the novel active moiety in sodium picosulfate throughout judicial review of the agency's denial of NCE exclusivity for Prepopik.[20] The issue in the case was whether the presence of previously approved drug substances in Prepopik rendered the new active moiety, picosulfate, ineligible for NCE exclusivity. The administrative record in the case included numerous statements and actions by FDA confirming that Prepopik contains a new (*i.e.,* not previously approved) active moiety. The agency (through counsel) unequivocally represented to the court that Prepopik

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> If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

[16] Again, the agency was well aware at this time that sodium picosulfate and bisacodyl had a common active metabolite, BPHM. Nevertheless, FDA did not list NDA 021551 for Halflytely, a previously approved product that contains bisacodyl and for which FDA considers BPHM to be the active moiety.

[17] FDA Petition Response, Docket Nos. FDA-2013-P-0058, FDA-2013-P-0119 and FDA-2013-P-0471 (Feb. 20, 2014) (Response to Citizen Petition) at 3.

[18] FDA Petition Response, Docket Nos. FDA-2013-P-0058 and FDA-2013-P-0119 (Oct. 10, 2014) (Response to Petition for Reconsideration) at 1 ("After Gilead's petition was filed, Ferring put forth a similar contention for its fixed-combination Prepopik (NDA 202535), that contains picosulfate, which was a new active moiety at the time of approval.").

[19] No other stakeholder proposed in the public docket for the petition proceeding that Prepopik should be denied NCE exclusivity on the basis that picosulfate is an ester of a previously approved active moiety. This reinforces the understanding in the regulated community that the sulfur-based covalent appendages in Prepopik would not be considered esters under the FDA framework.

[20] *See, e.g.*, Defendants' Cross-Motion For Summary Judgment, *Ferring v. Burwell* at 22 ("Prepopik contained both a previously approved active moiety and a new active moiety in the same drug product") at 9 ("FDA determined that although Prepopik contained a new active moiety, picosulfate, that had not been previously approved in any NDA prior to the approval of Prepopik, it also contained a previously-approved active moiety and thus was not eligible for 5-year NCE exclusivity.").

contains a new active moiety.[21] And, the basis of the District Court's September 2016 opinion is that the agency's decision not to award Prepopik NCE exclusivity was arbitrary and capricious, given that Prepopik represented the first approval of the new active moiety, picosulfate.

Now, on remand to effectuate the District Court's decision, FDA suggests for the first time that the active moiety of sodium picosulfate may be BPHM. To reach this conclusion, the agency would have to take the position that the covalently bound sulfur-based groups in the picosulfate moiety should be excluded as esters. This, however, would be a complete reversal of the agency's prior analysis and all of its prior regulatory decisions for Prepopik, not to mention its litigation position. Given the amount of time the agency had to review the molecule, and the number of instances in which the agency ***concluded, relied upon and asserted that picosulfate is a novel active moiety***, it is not plausible to say that the agency simply made an error. Rather, the April 5 letter must be considered the product of a change in interpretation as to what it means to be an "ester" under the agency's framework. To spring this interpretation on Ferring now, without adequate notice, process or explanation, and after inducing a District Court to rely upon the agency's previous interpretation, would be arbitrary and capricious conduct in its purest form.

In this instance, we believe the best, most appropriate course is to evaluate the eligibility of Prepopik for exclusivity based on the interpretation the agency had in place at the time of Prepopik's approval, *i.e.*, that picosulfate is a novel active moiety. As the agency determined in 2014 in refusing to apply NCE exclusivity to Prepopik and other fixed-combination products containing novel active moieties, "[e]xclusivity runs from the date of approval of a drug product."[22] Accordingly, FDA refused to apply to Prepopik (and to other similarly-situated products) the agency's new interpretation, "which we had not announced prior to the approval of these products."[23] In particular, FDA was concerned that other sponsors may have relied on the agency's previous interpretation. Here, Ferring has relied on the agency's consistent determination over nearly eight years that picosulfate is a novel active moiety. For these reasons, the most defensible approach is for the agency to base its analysis of the picosulfate active moiety on the interpretation the agency used at the time of Prepopik's review and approval.

II. FDA Correctly Determined that Picosulfate is Not an Ester for FDA Regulatory Purposes

FDA's original analysis was the correct analysis. Esters are commonly understood to be a class of organic compounds formed by the reaction between a (carboxylic) acid and alcohol resulting

[21] *Id.*

[22] Response to Citizen Petition at 17. *See* discussion *infra* at III.

[23] *Id.*

in a functional group with a central carbon atom.[24] Where the agency has had occasion to give meaning to the term, FDA has recognized that esters contain a central carbon atom or a central atom that is "usually" carbon.[25] To our knowledge, FDA has never described the term "ester" as including functional groups with a central sulfur atom. Most important for purposes of the issue raised in the April 5 letter, the agency officials who reviewed the structure of sodium picosulfate on multiple occasions, and based their regulatory decisions on the structure of sodium picosulfate, never identified or recognized the picosulfate moiety as an ester.

The characteristics of sulfur-based functional groups are different than carboxyl groups. Sulfur atoms are significantly larger than carbon atoms, can be present in multiple oxidation states, and form up to four bonds with oxygen, two double bonds and two single bonds. By contrast, carboxyl esters contain a central carbon double-bonded to an oxygen atom and single-bonded to a second oxygen atom. As a result, metabolism of sulfur-based appendages may be different than routine hydrolysis of carboxyl esters. That is precisely the case with sodium picosulfate, which is metabolized by gut bacteria rather than by an endogenous esterase enzyme.[26] For example, Eubacterium A-44 is a sulfotransferase present in human intestinal flora that has been identified as an important catalyst in the transformation of picosulfate into BPHM.[27] The regulatory distinction between sulfur-based functional groups and carboxyl esters is therefore rooted in key differences with regard to the chemistry and pharmacology of these appendages.

FDA has given no reason to explain why it should abandon its prior views regarding Prepopik. Nothing has changed about the chemistry or identity of sodium picosulfate, both of which have been well known to the agency for years. Accordingly, the agency can and should evaluate Prepopik's exclusivity based on its previous conclusion that picosulfate is a novel active moiety.

III. FDA Must Recognize NCE Exclusivity for Prepopik Based on its Conduct Before the District Court

FDA must implement the District Court's decision by recognizing NCE exclusivity for Prepopik. The agency's contemplated last-minute about-face on both the identity of the active moiety in

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[24] *See, e.g.,* Merriam-Webster, https://www.merriam-webster.com/dictionary/ester.

[25] FDA Mem. in Opp. to Motion for Summary Judgment, *Actavis Elizabeth LLC v. Sebelius* (D.D.C. Dec. 18, 2009) at 6 ("Amides and esters have undisputed structural differences. An amide contains a central carbon (usually carbon) attached to both an oxygen atom and a nitrogen atom. ***An ester contains a central carbon atom attached to two oxygen atoms***.") (emphasis added); Brief for the Federal Appellees, Actavis Elizabeth LLC v. FDA (D.C. Cir. June 9, 2010) at x (defining an ester as "a covalent bond in which an oxygen 'O' atom is linked to a central (***usually carbon or 'C') atom that is double bonded to an oxygen 'O' atom***") (emphasis added).

[26] D-H. Kim, et al., *The Role of Intestinal Bacteria in the Transformation of Sodium Picosulfate*, 59 JAPAN. J. PHARMACOL. 1992 at 1-5.

[27] *Id.* at 4-5.

sodium picosulfate and the question of whether the active moiety had previously been approved would be unlawful in light of the District Court's decision. FDA's proposed action would violate the law of the case and principles of estoppel, would fly in the face of the District Court's decision, and would exceed the scope of the District Court's remand. As previously noted, FDA consistently took the position throughout the administrative record on both Prepopik's NCE exclusivity determination and Prepopik's approval that the active moiety in sodium picosulfate was picosulfate, and that it had never previously been approved. FDA also repeatedly took those same positions throughout the District Court case, leading the District Court to issue a reasoned decision that was built entirely around those factual predicates. Having done so, the agency simply has no authority to provide a novel interpretation of these critical factual issues on remand.

IV. Conclusion

For the reasons stated above, FDA appropriately recognized picosulfate as a novel active moiety, and has failed to provide a reasoned basis for reversing its prior determination. The chemical structure of picosulfate has been known to the agency for nearly eight years. The April 5 letter provides no new information that would warrant an entirely new characterization of the picosulfate active moiety. Awarding NCE exclusivity to Prepopik is the only outcome that appropriately recognizes the reliance that Ferring and the District Court placed on the agency's prior determinations. It is also a scientifically sound decision based on the common understanding of an ester and the original application of that understanding to picosulfate.

Finally, the April 5 letter indicates that FDA has provided "other stakeholders" an opportunity to provide views on Prepopik's exclusivity award. Accordingly, we request that the agency promptly disclose to Ferring all submissions made by other parties in response to the agency's April 5 letter and provide Ferring an opportunity to reply before the agency takes any action that would result in a denial of NCE exclusivity for Prepopik.[28]

Sincerely,

David M. Fox
Hogan Lovells US LLP
David.fox@hoganlovells.com
Tel: 202.637.5678

Susan M. Cook
Hogan Lovells US LLP
Susan.cook@hoganlovells.com
Tel: 202.637.6684

[28] We note that submissions of other parties regarding Ferring's drug product are not likely to contain confidential commercial or trade secret information. For this reason, FDA should be able to immediately disclose these submissions to Ferring.

Cc: Shoshana Hutchinson
Office of the Chief Counsel

Erik Thygesen
Director, US Regulatory Affairs
Ferring Pharmaceuticals Inc.