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VIA HAND DELIVERY - RETURN RECEIPT REQUESTED

January 29, 2013

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

Citizen Petition

The undersigned, counsel for Ferring Pharmaceuticals, Inc. ("Ferring"), submits this petition in accordance with § 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA")[1], as well as 21 C.F.R. §§ 10.20, 10.30, and 314.108, requesting that the Commissioner of Food and Drugs amend the exclusivity period granted for Ferring's Prepopik™ (citric acid; magnesium oxide; sodium picosulfate) oral solution drug product (new drug application ("NDA") 202535) under FFDCA §§ 505(c)(3)(E) and 505(j)(5)(F). We also request that the Food and Drug Administration ("FDA") stay acceptance of any abbreviated new drug application ("ANDA") or § 505(b)(2) NDA that references NDA 202535 and further stay any approval of such drug should any application be accepted until this critical question about the exclusivity period is addressed.

[1] 21 U.S.C. §§ 201 et seq. (hereinafter all citations will be to the FFDCA).

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Ferring requests that the Commissioner expedite the review of this petition if necessary to ensure that the requested relief occurs prior to acceptance or approval of any ANDA or § 505(b)(2) NDA that references Prepopik™.

NDA 202535 was approved on July 16, 2012, for cleansing of the colon as a preparation for colonoscopy in adults. The drug contains sodium picosulfate, a stimulant laxative, in combination with magnesium oxide and anhydrous citric acid. Magnesium oxide and anhydrous citric acid combine in the body to form magnesium citrate, an osmotic laxative. Sodium picosulfate is a novel active ingredient that has never been a component of an approved NDA. Both magnesium oxide and citric acid are prodrugs of the active ingredient magnesium citrate, and both have previously been components of approved NDAs.[2] FDA erroneously granted a three-year period of exclusivity to Ferring for Prepopik™ under FFDCA §§ 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) based on the grounds that the previous approvals for magnesium oxide and citric acid precluded granting five-year exclusivity under FFDCA §§ 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) for drug products containing novel active ingredients. As discussed in detail below, law, policy, and fairness require FDA to reconsider its decision and grant a five-year exclusivity period for Prepopik™.

I. Introduction

We request that FDA change the exclusivity period for NDA 202535 for Prepopik™ from the three-year period under FFDCA §§ 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) to the five-year period under FFDCA §§ 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii). In conjunction with this request, we further request that the Agency stay the acceptance of any submission and approval

[2] See, e.g., NDA 018519 for Baxter Healthcare's discontinued citric acid, magnesium oxide, and sodium carbonate irrigation solution.

of any ANDA or § 505(b)(2) NDA for generic versions of Prepopik™ pending review of and response to this petition. FDA must consider the unique circumstances surrounding Prepopik™. Failure to grant a five-year exclusivity period for Prepopik™ would be contrary to the intent of the Drug Price Competition and Patent Term Restoration Act of 1984 ("Waxman-Hatch Amendments")[3] and inconsistent with prior Agency actions and statutory interpretations regarding drug approval and exclusivity for innovative products.

FDA should reverse the decision regarding the exclusivity period for Ferring's Prepopik™ drug product, and grant five years of exclusivity based on the following:

- The intent of the Waxman-Hatch Amendments to the FFDCA, which clearly and unequivocally intended to reward innovators who developed drug products that contain novel active ingredients.
- The longstanding public policy position for avoiding duplicative clinical research. This issue raises practical resource utilization and ethical concerns, and it led to creation of FDA's current policies on § 505(b)(2) NDAs and hybrid new animal drug applications ("NADA") as a model for administrative rationality and precedent.
- Current grants of five-year (or greater than three-year) exclusivity to some drugs that are combinations of novel active ingredients with previously approved active ingredients in cases where there is remaining five-year exclusivity for the approval of the single ingredient version of the drug.
- Grants of exclusivity for NDAs that are approved where animal studies are used in place of human studies if human studies are deemed unethical. In these cases, drugs are approved and exclusivity may still be granted despite statutory requirements for human clinical studies. These approvals provide another example of administrative reasonableness and flexibility.

II. Background

The Waxman-Hatch Amendments created the foundation for the current generic drug approval and proprietary rights enforcement system that balances the protection of innovator's intellectual property and research investment in new drugs with the need for the timely approval

[3] The Drug Price Competition and Patent Restoration Act of 1984, Pub. Law No. 98-417, 98 Stat. 1598 (September 24, 1984).

of lower-cost generic drugs. One key to this balance is the use of time-specific periods of market exclusivity for novel NDA drug products against approval of ANDAs and § 505(b)(2) NDAs that reference the innovator NDA.

An original NDA approval requires, in pertinent part, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."[4] Conduct of such investigations is time-consuming and expensive. Protection for the significant investment in research time and expense comes in the form of patent term extensions, stays of approval for pending patent litigation, and, the most relevant to this petition, the grant of a three-year and a five-year term of market exclusivity where FDA may not approve a competitor's ANDA or § 505(b)(2) NDA if the application references the innovator's NDA or relies on a finding of its safety and effectiveness. Where, as here, there are no currently listed patents, the market exclusivity is the most important element of the drug product's intellectual property.

The five-year exclusivity term is available where the innovator's NDA is for a drug product that represents a novel drug, *i.e.*, one that uses an active ingredient that has not been previously approved in a § 505(b) NDA.[5] The three-year exclusivity term is available where the NDA is for a drug that uses an active ingredient that has been previously approved under § 505(b) and where clinical trials were necessary for the new drug product's approval.[6] The statutory language is convoluted, stating that five-year exclusivity applies:

[4] FFDCA § 505(b)(1)(A).
[5] FFDCA §§ 505(c)(3)(E)(ii), 505(j)(5)(F)(ii).
[6] FFDCA §§ 505(c)(3)(E)(iii), 505(j)(5)(F)(iii).

> If an application submitted . . . for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved.[7]

This phrasing is awkward and appears to create a degree of ambiguity as to whether Congress intended to confer the five-year exclusivity period on drugs that contain any novel active ingredients or whether that five-year exclusivity period was limited to drugs that contain only novel active ingredients. This petition concerns the exclusivity term that is appropriately granted to an NDA for a new drug product that includes a combination of a novel active ingredient together with previously approved active ingredients.

FDA's implementation of the exclusivity term provisions of the Waxman-Hatch Amendments is found at 21 C.F.R. § 314.108. In these regulations, FDA uses the term "active moiety" in place of the statutory term "active ingredient," introduces the term "new chemical entity" ("NCE"), and expands the definition of what is considered to be the same active ingredient or moiety.[8] The regulations first define an NCE as "a drug that contains no active moiety that has been approved by FDA in any other application submitted under § 505(b) of the act."[9] The same regulation defines "active moiety" as:

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[10]

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[7] FFDCA §§ 505(c)(3)(E)(ii), 505(j)(5)(F)(ii).

[8] We note that FDA's regulation defining "active moiety" goes beyond the express terms of the statutory language defining "active ingredient" for purposes of determining when a drug is eligible for five-year exclusivity. This regulation provides one example where FDA goes beyond the apparent plain meaning of the statute to further its regulatory aims. FFDCA §§ 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) both define "active ingredient" by including "any ester or salt of the active ingredient" for exclusivity purposes. FDA regulations at 21 C.F.R. § 314.108 expand this considerably and consider active ingredient (e.g., "active moiety") to include not only the salt or ester, but also "other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule." This expansion of the definition serves to limit the availability of five-year exclusivity and does not appear to be based on any articulated Congressional intent.

[9] 21 C.F.R. § 314.108(a).

[10] Id.

FDA regulations then restrict the five-year exclusivity term to "a drug product that contains a new chemical entity."[11] In the case of Prepopik™, FDA interprets its regulation and the statute as restricting the five-year exclusivity term to only products containing active moieties (active ingredients) that have never been approved, alone or in combination, in any §505(b) NDA. FDA's interpretation of the statutory provisions related to exclusivity for drugs with a combination of novel and previously approved active ingredients has not been the subject of any comprehensive formal analysis or discussion, and there does not appear to have been any litigation regarding the issue. FDA's interpretation of its regulations with regard to Prepopik™ lacks articulated reasons or analysis, and is unreasonable, arbitrary, and capricious in light of the clear statements of Congressional intent in support of a broad applicability of five-year exclusivity to drugs with novel active ingredients,[12] the clear public interest of rewarding developers of drug products containing novel active ingredients, and prior Agency actions in related administrative areas.

III. Prepopik™ History

Prepopik™, NDA 202535, was approved on July 16, 2012, and the drug is "a combination of sodium picosulfate, a stimulant laxative, and magnesium oxide and anhydrous citric acid which form magnesium citrate, an osmotic laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults."[13] The drug is supplied as two packets of powder that are dissolved in water prior to administration. The magnesium oxide/citric acid component react in solution to form magnesium citrate, which is an osmotic agent that causes water to be retained within the gastrointestinal tract. The sodium picosulfate component

[11] 21 C.F.R. §314.108(b)(2).
[12] See, e.g., Report accompanying H.R. 3605, June 12, 1984, p. 29.
[13] Propopik labeling as of the date of NDA approval.

stimulates colonic peristalsis. The combined effect of the two laxative agents has been found by FDA to be safe and effective as a pre-colonoscopy colon cleanser. The magnesium oxide/citric acid components had been previously approved in NDAs as active ingredients in other laxative drug products. Sodium picosulfate represents a novel active ingredient that has not been contained in any approved drug product.

FDA's approval was based, in part, on the results of two randomized, controlled clinical studies of a total of approximately 1200 patients (1195 were included in the primary efficacy analysis). The studies demonstrated non-inferiority compared to approved colon cleanser products. In addition to the two clinical studies, FDA's approval included a requirement for three post-marketing pediatric studies. The required studies and post-approval requirements were of the magnitude typically required for drugs containing novel active ingredients and represented significantly more investment of time and effort than is usually necessary for approvals for drug products that contain only previously approved active ingredients.

Prepopik™ is a combination drug that contains more than one active ingredient. Under FDA's combination drug policy, when

> [t]wo or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.[14]

FDA generally requires studies (factorial studies) to evaluate the individual contribution to the overall efficacy of the drug under review. With Prepopik™, FDA determined that:

> A full factorial study would not be required to address the combination rule. Both components to this combination product are cathartics with different mechanisms of action that each have colon cleansing effects. After examining the literature for evidence of the effectiveness of each component for colon cleansing, the

[14] 21 C.F.R. § 300.50(a).

> reviewers concluded that a full factorial study could not be conducted due to serious ethical concerns because the literature review indicated that each component as a stand alone would result in inadequate colon cleansing for colonoscopy.[15] (emphasis added)

FDA, therefore, determined that a single ingredient arm in the clinical trials would be inappropriate due to ethical concerns.[16] Similarly, if approval was sought for a single ingredient drug containing the active ingredient sodium picosulfate, that approval would also present significant ethical concerns. As noted by FDA reviewers, the ingredient, as a stand-alone drug, would result in inadequate colon cleansing, and it would not likely be deemed safe and effective. Under current FDA policy, all active ingredients of a drug product must be novel active ingredients if the drug is to qualify for a five-year marketing exclusivity period. A novel active ingredient such as sodium picosulfate, which is not suitable for single ingredient drug use as a colon cleanser, cannot qualify for five-year exclusivity because it must be paired with other active ingredients to obtain fully efficacious results. This interpretation and policy is inconsistent with the statutory intent of the Waxman-Hatch Amendments to reward innovation, precedent, and fundamental fairness to the drug developer.

IV. Arguments

A. FDA's denial of five-year exclusivity for Prepopik™ is inconsistent with the statutory intent of the Waxman-Hatch Amendments.

§§ 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FFDCA state:

> If an application submitted . . . for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . , no application which refers to the drug . . . may be submitted under subsection (b) of this section before the expiration of five years . . . .[17]

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[15] NDA number 202535 Prepopik™, Division Director Summary Review, Donna Griebel, MD, p. 40, July 16, 2012.
[16] Id.
[17] FFDCA § 505(c)(3)(E)(ii).

and

> If an application submitted . . . for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . , no application may be submitted under this subsection [505(j)] which refers to the drug for which the subsection (b) application was submitted before the expiration of five years . . . .[18]

These sections together provide the statutory basis for the five-year exclusivity period for innovative drug products that contain new active ingredients that have not been previously approved by FDA. The statute also states that no § 505(b)(2) NDA or ANDA may be submitted during the five-year exclusivity period except that these applications could be submitted after four years if they contain a certification of patent invalidity or noninfringement.[19]

This five-year exclusivity is complemented by a three-year exclusivity term (found at FFDCA §§ 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii)) for new drug products that contain previously approved active ingredients. The difference in exclusivity terms is intended to provide a greater period of exclusivity for drug products that introduce novel drug ingredients to encourage their development. Drug products that introduce novel drug ingredients usually require a far more significant time and resource investment to bring to market than those drug products that either utilize previously approved active ingredients or that represent minor changes to already approved drug products. FDA confirms the reason for the difference in exclusivity terms in the 1989 proposed regulations for implementation of the Waxman-Hatch new drug provisions. In the preamble to that proposed rule, FDA, citing legislative history of the Waxman-Hatch Act, states:

> FDA's interpretation of the scope of the 5-year exclusivity provision is also consistent with the legislative history, which reveals that Congress was aware of

[18] FFDCA § 505(j)(5)(F)(ii).
[19] FFDCA §§ 505(c)(3)(E)(ii), 505(j)(5)(F)(ii).

> FDA's classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds.[20]

The principle of greater market exclusivity for new chemical entities that had not been previously approved started with the 10 year exclusivity provision granted to NDA approved for these drugs between 1982 and 1984. The United States Court of Appeals for the District of Columbia stated that Congress intended to provide a longer period of exclusivity where the drug product included an active ingredient that had not been previously approved and required new research efforts:

> The Court stated Congress thereby sought to encourage innovation in the drug industry, by rewarding a pioneer drug with a ten year exclusivity, while protecting customers from unduly high prices by refusing to give a long period of market exclusivity to drugs which require no new research efforts.[21]

The Congressional record itself is replete with statements that support a longer term of market exclusivity for drug products containing novel active ingredients. Report language intended to explain the statutory language states:

> FDA may not make effective the approval of an ANDA for a drug including an active ingredient (including any ester or salt of the active ingredient) which was approved for the first time in an NDA between January 1, 1982 and the date of enactment of this bill until 10 years after the date of approval of the NDA.[22]

This explanatory language clearly and unequivocally states that the longer exclusivity period against ANDA approval applies where the drug product contains a never before approved active ingredient – in direct contradiction to FDA's interpretation of the novel drug exclusivity provisions. The above case and the report are discussing the ten-year exclusivity period that

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[20] 54 Fed. Reg. 28,871, 28,898 (July 10, 1989). In support, FDA cites the statement of Representative Waxman found in the Congressional Record (Cong. Rec. H9124 (September 6, 1984)), and statements found in House Report 857 Part I, 98th Cong., 2d Sess. 38 (1984).

[21] Abbott Laboratories v. Young, 920 F.2d 984 (D.C. Cir. 1990). The court was addressing the ten-year exclusivity available for drugs containing new active ingredients that were approved between January 1, 1982, and enactment of the Waxman-Hatch Act in 1984 found in FFDCA § 505(j)(4)(D)(i).

[22] Report accompanying H.R. 3605, June 12, 1984, p. 29. This section of the report refers specifically to the ten-year exclusivity term under FFDCA § 505(j)(5)(F)(i); however, the statutory language of this section is directly analogous to the language of FFDCA § 505(j)(5)(F)(ii).

applies to drugs approved "in the window" (i.e., between January 1, 1982 and September 24, 1984), but the language in the statute is identical and equally applicable to the five-year exclusivity provisions. The language does not in any way suggest that the exclusivity would not apply simply on the basis that the drug included a previously approved active ingredient in addition to the novel ingredient. Indeed, such an approach would hardly further the goal of rewarding innovation. Such a limitation would have been important enough to at least merit discussion or explanation. Instead, such a limitation is not mentioned even once in the entire legislative history of the Waxman-Hatch Amendments.

The explanatory language for the five-year exclusivity against § 505(b)(2) approval is similar to that of the exclusivity against ANDA approval:

> FDA may not make effective the approval of a Paper NDA [§ 505(b)(2) NDA][23] for a drug including an active ingredient (including any ester or salt of the active ingredient) which was approved for the first time in an NDA between January 1, 1982 and the date of enactment of this bill until 10 years after the date of approval of the NDA.[24]

In addition to the Committee report, there are also statements from the pharmaceutical industry that provide the industry's understanding of the exclusivity at the time of enactment of the statute. The statutory language and particularly the exclusivity provisions were carefully negotiated between the pioneer drug companies, the generic industry, and FDA. Therefore, industry's view offers valuable insight into the intended meaning of statutory language. One illustrative statement comes from American Home Products:

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[23] See, Report accompanying H.R. 3605, August 1, 1984, p. 19, defining "Paper NDA" as an NDA approved under FFDCA § 505(b), for which the sponsor does not have the right of reference for necessary studies.

[24] Report accompanying H.R. 3605, June 12, 1984, p. 34. This section of the report refers specifically to the ten-year exclusivity term under FFDCA § 505(c)(3)(E)(i); however, the statutory language of this section is directly analogous to the language of FFDCA § 505(c)(3)(E)(ii).

> The bill would permit marketing exclusivity for 10 years only for active ingredients first approved between January 1, 1982 and the date of enactment of the bill.[25]

The industry understanding of the exclusivity provisions was that the longer (five and ten year) exclusivity terms were granted for active ingredients first approved in an NDA. There was no limitation that this exclusivity did not apply if the drug product also included previously approved active ingredients. Again, this view is not contradicted anywhere in the legislative history.

The exclusivity provisions were raised during floor debate as well. Again, the statements are consistent with the view that the longer exclusivity term is applicable when a drug includes a novel active ingredient and is not limited in any way by the presence of an additional, previously approved active ingredient:

> First, the amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of this legislation. This provision gives the drug industry incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains.[26]

Here, Representative Waxman explains the intent to reward development of drugs containing innovative ingredients. He specifically notes the importance of this exclusivity incentive for drugs (like Prepopik™) that have no remaining patent exclusivity. Note that in this context, the term "new chemical entity" does not refer to the FDA regulatory definition found at 21 C.F.R. § 314.108(a). That regulatory definition post-dates the Waxman-Hatch Amendments, and it was first proposed by FDA in the 1989 ANDA regulations.[27] Congress would have used the term as it was used in 1984, prior to FDA's ANDA regulations. In 1984 and earlier, the term "new

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[25] Hearings on H.R. 3605 before the Judiciary Committee of the House of Representatives, Subcommittee on Courts, Civil Liberties, and the Administration of Justice, March 28, April 26, and June 6, 27, 1984, position paper of American Home Products Corporation, p. 993.

[26] Statement of Representative Waxman found in the Congressional Record (Cong. Rec. H9113 (September 6, 1984)).

[27] 54 Fed. Reg. 28,871 (July 10, 1989).

chemical entity" was used by FDA as equivalent to "novel active ingredient." For example, in 21 C.F.R. § 299.4, the regulation for established drug names:

> All applicants for new-drug applications and sponsors for "Investigational New Drug Applications" (IND's) are encouraged to contact the USAN Council for assistance in selection of a simple and useful name for a new chemical entity. Approval of a new-drug application providing for the use of a new drug substance may be delayed if a simple and useful nonproprietary name does not exist for the substance and if one is not proposed in the application that meets the above-cited guidelines.[28]

It is clear from this regulation that the term "new chemical entity" refers to an individual "new drug substance" or ingredient, and not to the entire or all active component(s) of the drug product. The regulation anticipates that USAN will provide a "useful nonproprietary" name for the "new chemical entity," something that is done for individual ingredients, not combinations of active ingredients. Other uses of the term "new chemical entity" found in the Federal Register similarly support the proposition that the term applied to an individual active ingredient, and not combinations of active ingredients.[29] We find no instance in the pre-Waxman-Hatch Amendments record of any use of the term that is in reference to multiple active ingredients.

In contrast, it is clear from other statements in the Congressional Record that the three-year exclusivity term was intended to apply to drugs that contain only non-novel active ingredients. For example:

> First, under this proposal, a drug company whose patent is going to expire could – under some circumstances – conduct short, simple, noninnovative, clinical trials and seek FDA approval for an over-the-counter version of the drug. Under this proposal, even though this change would not affect patent status, the drug company would receive a "reward" of 3 years of marketing exclusivity.[30]

and

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[28] 21 C.F.R. § 299.4(d).
[29] See, e.g., 39 Fed. Reg. 33,134 (Sep. 13, 1974); 42 Fed. Reg. 57,160 (Nov. 1, 1977); 45 Fed. Reg. 82,052 (Dec. 12, 1980).
[30] Statement of Representative Kastenmeier found in the Congressional Record (Cong. Rec. H9114 (September 6, 1984)).

> The 3-year protection, in effect, provides that a product that is not a new chemical entity would be protected for 3 years after the FDA approval because there were essential clinical trials submitted to FDA, and only when clinical trials were submitted.[31]

Both of these statements demonstrate that the Congressional understanding of the three-year exclusivity was for drugs that were viewed as including only previously approved active ingredients. There is no mention in these statements, or elsewhere in the legislative history, of applying the three-year exclusivity period to drugs that contain a combination of novel and previously approved active ingredients. The only discussion is in regard to whether it is sound policy to provide three-years of exclusivity to drugs that do not contain novel active ingredients. Again, these exclusivity provisions were discussed at length and carefully negotiated. FDA's current position with regard to Prepopik™ is inconsistent with the clear understanding in the legislative record.

It is, therefore, well-established and accepted from the legislative history that the goal of the five-year exclusivity period is to encourage pharmaceutical innovation by rewarding those sponsors that bring drugs containing novel active ingredients to market. FDA's interpretation requiring all ingredients in a combination drug product to be novel ingredients is contrary to this intent and thus unreasonable, arbitrary, and capricious.

B. Failure to provide five-year exclusivity for Prepopik™ is inconsistent with the policy to minimize duplicative studies.

For decades FDA policy and practice have focused on reducing unnecessary and duplicative clinical research in drug development and approval. This point is clearly illustrated in the Agency's interpretation of FFDCA § 505(b)(2) and the similar policy with regard to animal drug development and approval – the hybrid new animal drug application ("NADA"). In

[31] Statement of Representative Waxman found in the Congressional Record (Cong. Rec. H9121 (September 6, 1984)).

both cases, the Agency created abbreviated mechanisms for approval of modifications to existing drugs without requiring the applicant to first seek approval of a duplicate of the reference listed drug product. The same policy reasons that support FDA's interpretation of the § 505(b)(2) NDA and hybrid NADA also support granting five-year exclusivity for combination drug products that contain both novel and previously approved active ingredients.

1. The FFDCA §505(b)(2) NDA and the Phantom ANDA

The Waxman-Hatch Amendments significantly expanded the potential usefulness of FDA's "paper NDA" policy[32] by establishing FFDCA § 505(b)(2). Prior to September 24, 1984, FDA had created a mechanism for approval of NDAs for drugs that were essentially copies of drugs that were first approved after the Drug Amendments of 1962.[33] This paper NDA mechanism was limited, however, and could only be used for "generic" copies of a small subset of the post-62 NDA approved drugs. The §505(b)(2) NDA created by the Waxman-Hatch Amendments[34] provides much more flexibility, and permits NDA approval for a wide range of drug products. This type of application falls between the § 505(b)(1) NDA and the ANDA.

With the § 505(b)(1) NDA, the sponsor must demonstrate the safety and effectiveness of the drug using data owned by the sponsor (or to which the sponsor has right of reference). An ANDA applicant relies on the finding of safety and effectiveness made for the reference listed drug, and it need only demonstrate bioequivalence to the reference drug. An application filed under §505(b)(2) must still demonstrate safety and effectiveness for its drug product, but it can rely on certain investigations required for approval of the drug that "were not conducted by or for

[32] For an explanation of the original Paper NDA policy, see, Memorandum of Marion Finkel, Associate Director of the Bureau of Drugs, as republished at 46 Fed. Reg. 27,396 (May 19, 1981).
[33] Drug Amendments Act of 1962, Public Law 87-781, 76 Stat. 780 (1962).
[34] Some confusion over what is meant by the term "Paper NDA" has been caused by the reference to § 505(b)(2) NDAs as "Paper NDAs" in several places in the Waxman-Hatch legislative history. The Paper NDA properly refers to FDA's administratively created mechanism for approval of generic versions of NDAs approved between 1962 and 1984.

the applicant, and for which the applicant has not obtained a right of reference or use."[35] Among other things, this approach permits reliance on the FDA finding of safety and effectiveness for the reference drug (as is done with ANDAs). § 505(b)(2) had been interpreted in a way that permits a great deal of flexibility to drug sponsors. The § 505(b)(2) application has permitted approval of applications that have had very little original clinical data and relied almost entirely on the findings of safety and efficacy for already approved drugs[36] as well as applications for drugs for NCEs that rely almost entirely on original studies and data.

Shortly after enactment of the Waxman-Hatch Amendments, there was significant debate over how much flexibility §505(b)(2) provided to a sponsor. Some pioneer drug companies took the position a competitor drug company must first submit an ANDA to the pioneer drug before that competitor could seek approval of any modification or change to that drug through the § 505(b)(2) process. FDA issued a policy letter in 1987 (referred to as the "Parkman Letter") that stated that any narrow interpretation of FFDCA § 505(b)(2) "would be a disincentive to innovation and require needless duplication of research."[37] The § 505(b)(2) policy was confirmed and expanded through the 1989 proposed[38] and 1994 final regulations[39] implementing the Waxman-Hatch Amendments. In explaining the policy, FDA has more recently clearly affirmed this view, and summarized the position stated in the original Parkman Letter:

> The Agency also rejected the option of requiring the submission and approval of an ANDA, followed by a supplement to that ANDA containing the data necessary to support the change. The Agency noted that to generate all of the stability and other data required for ANDA approval, the sponsor would have to take steps to manufacture a product that it had no intention to market. The Agency concluded that the better course was to permit submission of an application under section

[35] FFDCA § 505(b)(2).
[36] See, e.g., NDA 22-442 SN016 for Rezira™. FDA relied upon previous findings of safety and efficacy for the product including findings in the over-the-counter cough/cold monograph that pseudoephedrine was generally recognized as safe and effective. Clinical Review, NDA 22-442, Xu Wang, M.D., Ph.D., Dec. 8, 2010, p. 4.
[37] Letter to Industry from Paul Parkman, Acting Director, Center for Drugs and Biologics (April 10, 1987).
[38] 54 Fed. Reg. 28,871 (July 10, 1989).
[39] 59 Fed. Reg. 50,338 (Oct. 3, 1994).

> 505(b)(2) for a change to an already approved drug product *without* requiring that the application first obtain approval of an ANDA (the phantom ANDA).[40] [emphasis in the original]

FDA's position benefits the public in a number of ways: it reduces company drug development expenditures; decreases time to market for new drug products; eliminates the ethical concerns raised by duplicative clinical trials; and conserves Agency reviewer resources.

The same situation exists here. FDA's reviews concluded that conducting clinical trials for a single ingredient sodium picosulfate drug would be unethical.[41] Thus, it would not be possible to approve a single ingredient sodium picosulfate drug for the approved indication. Additionally, even if approval of a single ingredient sodium picosulfate drug were possible, requiring such approval in order for the sponsor to obtain the five-year exclusivity that is intended to reward innovation would be against public policy for the very reasons FDA articulated in the Parkman Letter and § 505(b)(2) rulemaking. Two applications would be required – one NDA for the single ingredient drug to obtain five-year exclusivity, and a second NDA for the marketed multi-ingredient drug. This process would increase company drug development expenditures; increase time to market for new drug products; raise significant ethical concerns by requiring unnecessary clinical trials; and waste Agency reviewer resources. The only appropriate ethical course of action is to grant the five-year exclusivity for drugs containing novel active ingredients, regardless of whether that drug also contains previously approved active ingredients. This course of action is particularly important in situations such as the approval of Prepopik™ where, according to the Agency, no approval of the novel single ingredient drug is possible. Failure to provide five-year exclusivity for Prepopik™ is inconsistent with the policy to minimize research that is duplicative and raises ethical concerns.

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[40] FDA Docket numbers 2000P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-04048/CP1, Response of FDA to petitioners, October 14, 2003.

[41] See, NDA 202535 Prepopik™, Division Director Summary Review, Donna Griebel, MD, p. 40, July 16, 2012.

2. The Hybrid NADA

The success of the Waxman-Hatch Amendments in reducing drug prices to consumers led to using the law as a model for changes to the animal drug approval system. The Generic Animal Drug and Patent Term Restoration Act of 1988 ("GADPTRA") was introduced in Congress several times in slightly different forms with the intent of bringing the Waxman-Hatch Amendments type of generic approvals to animal drugs. After two years and six different primary bills, GADPTRA was passed, but the new law was not a precise statutory duplicate of FFDCA § 505(b)(2). This lack of a precise duplicate of § 505(b)(2) created confusion in the regulatory system that restricted innovation among holders of generic animal drug approvals as well as specialty pharmaceutical companies creating new products.[42]

FDA rectified this situation by administratively creating its "(b)(1) supplement" for abbreviated new animal drug application ("ANADA") and "hybrid" application policies, *i.e.*, the animal drug equivalent to the Paper NDA or § 505(b)(2) application. FDA implemented the hybrid process for many of the same policy reasons as it did with the Paper NDA and the Agency's interpretation of FFDCA § 505(b)(2) – to avoid duplicative research costs, decrease drug costs to patients, reduce the burden on FDA resources, speed up the development of innovative drugs, and reduce ethical concerns raised by unnecessary testing.[43]

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[42] The legislative history of GADPTRA is not clear on why a specific §505(b)(2)-like provision was not included in the approved act; provisions that are worded closely to § 505(b)(2) were included in two early GADPTRA bills. Statements in the legislative record show that it was the clear intent of Congress for GADPTRA to mirror the Waxman-Hatch Amendments to the extent possible. The difference likely arose because the final GADPTRA bill was drafted by the Office of Legislative Counsel in the House of Representatives. The Waxman-Hatch Amendments were drafted in the Senate.

[43] See, GADPTRA Policy Letter number three, August 2, 1989 ("CVM believes that these interpretations would meet important goals of the generic legislation: to avoid duplicative research, to provide incentive for generic sponsors to innovate, and to make the conditions of use of the pioneer and generic drugs the same to the maximum extent possible.").

FDA published its (b)(1) supplement and hybrid NADA policies in its GADPTRA policy letters. There were seven of these letters in all, and two of them specifically addressed the hybrid application and (b)(1) supplement issues. The supplement process articulated in Policy Letter number three forms the basis for expansion of the policy into allowing "hybrid" applications, which were specifically addressed in the seventh and last of the GADPTRA Policy Letters.

The lack of a statutory parallel to FFDCA § 505(b)(2) in GADPTRA meant that there was no precise statutory basis for approval of an ANADA or any supplement that contains changes from the reference listed drug beyond changes permitted through the suitability petition process.[44]

Instead of mindlessly following restrictive statutory terms, which required either a full NADA or an ANADA that was a copy of a pioneer (or contained only the limited changes permitted by the suitability petition process), FDA created a new type of animal drug application that was not specifically identified in the statute. FDA looked to the underlying purpose of the statute as found in the legislative history, and found that the intent of Congress had been to create a parallel to the Waxman-Hatch Amendments, and this parallel included a process similar to the FFDCA § 505(b)(2) NDA.

FDA first permitted innovative changes to ANADA drug products through use of "(b)(1) supplements" to ANADAs. This process allowed holders of approved ANADAs to submit applications for changes far beyond those permitted under a narrow interpretation of the statutory language – *i.e.*, those that required animal testing other than bioequivalence testing. The Agency

[44] The suitability petition process does not permit changes for which new studies - other than bioequivalence studies - are required. 21 C.F.R. § 314.93.

then went on to expand the "(b)(1) supplement" concept and permitted changes from the reference drug without first requiring an original ANADA. This process, similar to the "phantom ANDA" policy found in the Parkman Letter on the human drug side, permitted what amounted to an administratively created § 505(b)(2)-like NADA.[45]

The hybrid NADA policy created applications that are considered to be both § 512(b)(1) and § 512(b)(2) applications for different statutory purposes. For example, the hybrid applicant must certify to any patents for the reference listed drug product and provide appropriate bioequivalence data (as required for an ANADA) and evidence of safety and effectiveness (as required for a NADA). Again, FDA acted to implement the intent of GADPTRA, without following the specific statutory terms.

The hybrid NADA and § 505(b)(2) policies clearly demonstrate that FDA will not be bound by statutory terms where those terms frustrate the clear intent of Waxman-Hatch or GADPTRA. FDA must demonstrate that same reasonable approach interpreting the ambiguous language of the five-year exclusivity provisions in a way that fulfills the Congressional intent. It must grant five years of exclusivity for the novel drug product Prepopik™.

3. Application of five-year exclusivity for Prepopik™

In the development of its policy on five-year exclusivity, FDA has acted in a manner that is not consistent with the development of its § 505(b)(2) and hybrid NADA policies. Currently, five-year exclusivity is blocked for those drug products that contain one novel active ingredient in combination with other previously approved active ingredients, but allowed for five-year

[45] GADPTRA Policy Letter number seven, March 20, 1991 ("FDA believes that a more consistent, less burdensome interpretation of the 1988 Amendments is to allow a generic applicant to submit a 512(b)(1) application for a change in an already approved animal drug that requires the submission and review of investigations conducted by or for the applicant, without first obtaining approval of the ANADA for a duplicate of the listed animal drug . . . . These applications will be known as 'hybrid' applications.").

exclusivity if an application is submitted for a drug product that includes only the novel active ingredient. This point would be true even if the drug product would be less safe or effective than the combination drug product. In some situations, such as with Prepopik™, a version of the drug containing only the novel active ingredient may not be effective unless combined with other active ingredients. Nevertheless, FDA's current policy would deny drugs like Prepopik™ five-year exclusivity despite the fact that it contains a novel active ingredient, and despite the fact that the clear intent of Congress was to reward sponsors of innovative new drugs with five years of exclusivity.

FDA, through its administrative actions, has acknowledged that if an NDA is submitted that contains only a novel active ingredient, then the five-year exclusivity that is granted would also apply to any subsequent approval of a combination drug product containing that novel ingredient in combination with a previously approved active ingredient. FDA would grant the first (single ingredient) NDA five-year exclusivity and the second NDA (for the combination ingredient drug) would also be protected by this same five-year exclusivity term. FDA's position is that no applicant could obtain §505(b)(2) NDA or ANDA approval to the second approved NDA (for the combination ingredient drug) until the first NDA's five-year exclusivity term expired. As a result, the second NDA may receive more than the three-year exclusivity term that would otherwise be granted.

The current policy, therefore, is contrary to public policy and is inconsistent with FDA's actions under the § 505(b)(2) and hybrid NADA policies discussed previously. FDA's exclusivity policy merely encourages companies that wish to market a combination product with novel and previously approved active ingredients to file two NDAs *(i.e.*, first one for the single ingredient NCE and then one with the combination) to ensure that it obtains five-year

exclusivity. This requirement is unnecessarily burdensome, duplicative, runs counter to the intent of the Waxman-Hatch Amendments, raises ethical concerns by requiring additional clinical trials, and serves no public purpose. In similar situations as discussed above with the § 505(b)(2)/Phantom ANDA and the hybrid NADA, FDA has enacted policies based on practical statutory interpretations that minimize the need for duplicative studies and drug applications. FDA must revise the five-year exclusivity policy to a rational one that advances the public interest and Congressional intent. The current policy position of FDA only results in unnecessary expenditure of resources, increased costs to consumers, longer delays in the creation of novel drug products, further increased burdens on FDA, and increased ethical concerns regarding the creation of unnecessary trials. That policy is unreasonable, arbitrary and capricious.

C. Failure to Provide Five -Year Exclusivity is Inconsistent with FDA grants of up to five years of exclusivity for drugs with a combination of ingredients based on previous approval of single ingredient drug.

On a number of occasions FDA has approved drug products with a combination of both novel and previously approved active ingredients where the drug product was granted more than three-years of exclusivity. Examples include, among others, the approvals for Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate tablets), and Valturna (aliskiren hemifumarate/valsartan tablets). In these situations, the exclusivity granted is based on the remaining five-year exclusivity term for single ingredient drug products containing the novel active ingredient.

Complera was approved under NDA 202123 on August 10, 2011. In FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), the drug product is listed as having five-year NCE exclusivity that expires on May 20, 2016. This grant of NCE

exclusivity is based on the exclusivity originally granted for Edurant (rilpivirine tablets), which was approved under NDA 202022 on May 20, 2011.

Valturna was approved under NDA 022217 on September 16, 2009. The Orange Book lists the drug product as having five-year NCE exclusivity that expired on March 5, 2012. This grant of NCE exclusivity is based on the exclusivity originally granted for Tekturna (aliskiren hemifumarate tablets), which was approved under NDA 021985 on March 5, 2007.

These approvals show that FDA does, in effect, grant five-year exclusivity protection to drugs that are combinations that contain previously approved active ingredients, so long as the single active ingredient drug containing the novel active ingredient is approved first. If these drug products were to be approved in the opposite order (i.e., the combination drug before the single ingredient drug), then under FDA's current policy neither drug would be eligible for a five-year exclusivity period. If the combination drug were approved first, then (under FDA's policy) it would only be eligible for three years of exclusivity because it contains previously approved active ingredients. If an NDA containing the novel ingredient from the combination drug is subsequently approved, then that NDA would also only be eligible for three years of exclusivity on the grounds that the active ingredient had been previously approved in the combination drug NDA. This policy is irrational and it runs counter to the public health goals of the Agency. The absurd result in the example above results in a situation where approval order of the single ingredient drug and the combination ingredient drug determines how much of a reward is due to the innovative drug sponsor, irrespective of the fact that the same amount of effort is expended.

D. Failure to Grant Prepopik five-year exclusivity is inconsistent with the tenet that the vagaries of the Order of NDA approval cannot alone create a reasonable statutory interpretation.

Statutory interpretations of the Waxman-Hatch Amendments that fail to address the intended purpose of Congress have been addressed by the courts. In one relevant case, the United States Court of Appeals for the District of Columbia was asked to address the question of when drug ingredients were considered to be the same for exclusivity purposes. Like the situation that is the subject of this petition, the court was faced with a question of a grant of exclusivity that appeared to be based on the order of NDA approval.[46] The statutory language states that five-year exclusivity applies to NDAs where "no active ingredient (including any ester or salt of the active ingredient)" has been previously approved. The court was asked to address whether Abbott Laboratories was entitled to five-year exclusivity for its drug where the salt version of the drug had been previously approved. Abbott argued that the plain meaning of the statute was that the base active ingredient was not a "ester or salt of the active ingredient" and therefore not the same active ingredient for statutory purposes. The court recognized this interpretation:

> To be sure, Abbott's interpretation, at first reading, is the more obvious linguistic construction of the statute--that active ingredient refers in this case to divalproex sodium. The parenthetical phrase ("including any ester or salt of the active ingredient"), according to Abbott, refers only to the original drug, the active ingredient "of which has been approved."[47]

However, the court went on to state:

> Abbott's interpretation then, unlike the FDA's, is possible linguistically but fails to serve any conceivable statutory purpose. It would mean that if an original drug application has an active ingredient in the form of a salt, a drug company cannot obtain extended protection by merely filing a new application for a drug with an active ingredient in its non-salt form, but if it does the reverse, as in this case, it

[46] Abbott Laboratories v. Young, 920 F.2d 984 (D.C. Cir. 1990).
[47] Id.

> can. That construction appears to be farfetched because it is not consistent with any legislative goal: Abbott can advance no hypothetical reason why Congress (or indeed any of the interest groups) would have wanted the degree of protection a drug received to turn on this variable sequence. Abbott's reading promotes neither the interests of the research-oriented pharmaceutical industry nor the generic drug industry in a rational way, producing instead a windfall depending on an accident of chemical nomenclature. We have not been offered any scientific, technical, economic or other explanation why Congress would intend the grant of a ten year market exclusivity to depend on the temporal sequence in which subsection (b) applications were approved and the counsel could not suggest any when pressed on this point. It appears, then, entirely serendipitous that in this case Abbott sought an application for the salt of valproic acid after first applying for valproic acid. Thus, under Abbott's interpretation, if a pharmaceutical manufacturer developed two usable drugs, one a salt of the other, he could gain extra protection by applying for approval of the acid first, followed by the salt, but not under the reverse sequence.[48]

The court called for a rational interpretation of the statutory language that would not depend on the vagaries of approval order. This same logic applies to the current situation. The degree of market protection for drugs containing novel active ingredients should not be dependent on whether the drug was first approved as a single ingredient drug or in combination with other, previously approved active ingredients. FDA has not advanced any rational reason that Congress would have denied five-year exclusivity to the novel NDA for Prepopik™ simply because the drug product contains novel as well as previously approved active ingredients.

FDA's policy that denies five-year exclusivity to drugs such as Prepopik™ encourages unnecessary clinical studies and administrative costs. Requiring a company to first acquire an NDA for a single ingredient drug product before obtaining an NDA for a combination including the novel active ingredient means that the applicant will most likely have to run unnecessary clinical studies in support of the single ingredient NDA. If the company plans on solely marketing a combination drug product, then these studies and review process are unnecessary

[48] Id.

and wasteful. FDA has previously acknowledged that such an approach does not make sense when it articulated its § 505(b)(2)/phantom ANDA and hybrid NADA policies.

Requiring unnecessary clinical trials may also violate ethical duties of medical practitioners. It may not be ethically feasible to conduct clinical trials on a single ingredient drug product simply for exclusivity purposes when a practitioner knows that the combination drug product will be more safe and effective.

Lastly, this policy would arbitrarily deny five-year exclusivity to those combination drug products that include a novel active ingredient that cannot support a finding of safety and efficacy as a single ingredient drug. If a single active ingredient drug product could not be found to be a safe and effective drug product on its own, then the applicant could not utilize the strategy of filing an NDA to the single active ingredient drug and then filing the NDA on the combination product that included the active ingredient. This ability of NCEs that can be found to be safe and effective on their own to utilize the five-year exclusivity provision when approved in a combination product appears to be an arbitrary distinction between NCEs that serves no public policy goal. Such inconsistencies are clearly contrary to the statutory intent of the Waxman-Hatch Amendments.

E. Failure to gran Prepopik™ five-year exclusivity is inconsistent with policy to grant exclusivity to NDA approvals based solely on animal studies data where human trials are unethical.

FDA's current position on five-year exclusivity runs counter to the position that it has taken regarding certain drug products whose approvals are supported solely through animal studies. In these cases, FDA showed how flexibility was necessary in order to ensure that unethical studies were not conducted in order to meet FDA's previously stated policy.

NDA approval under FFDCA § 505(b) requires that the drug sponsor provide (among other things) "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."[49]

The FFDCA expands on what is necessary to meet the "full reports of investigations" requirement by stating that the sponsor must provide "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[50] The Act goes on to state that:

> [T]he term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. (emphasis added)[51]

Thus the Act requires that "clinical investigations" be conducted in order for NDA approval under FFDCA § 505(b). The term "clinical investigations" has long meant human clinical studies. The legislative history of the Waxman-Hatch Amendments clearly shows that Congress intended exclusivity to apply to "human" clinical trials. In considering when exclusivity would apply, Congressman Waxman stated: "the only time where [drug products] will receive additional protection is when ... there were human clinical trials to justify the FDA approving that new drug application."[52] The courts have confirmed this interpretation.[53] Congress apparently never anticipated a situation where ethical concerns with human trials would result in approval based on animal studies.

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[49] FFDCA § 505(b)(1)(A).
[50] FFDCA § 505(d)(5).
[51] Id.
[52] Statement of Representative Waxman found in the Congressional Record (Cong. Rec. H9121 (September 6, 1984)).
[53] Zenith Laboratories, Inc. v. Bowen et al, Civ. A. No. 85-3646, 1986 WL 9886 L.D. N.J.)

FDA regulations and policy also have defined "clinical investigations" as efficacy studies[54] in humans. The FDA regulation that addresses new drug exclusivity defines "clinical investigation" as "an investigation in humans."[55]

Since as early as 1997, FDA publically acknowledged the shortcomings of the human clinical investigations requirement for certain drugs where efficacy trials in humans would be unsafe and constitute unethical practice. FDA created certain regulations for approval of new drugs when human efficacy studies are not ethical or feasible (this regulation is often referred to as the "Animal Rule").[56] Under this regulation, if

> definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance,[57]

then

> FDA may grant marketing approval for a new drug product for which safety has been established and for which the requirements of § 314.600 are met based on adequate and well-controlled animal studies when the results of those animal studies establish that the drug product is reasonably likely to produce clinical benefit in humans.[58]

In the Federal Register announcing the proposed rule, FDA acknowledged its traditional view on clinical investigations:

> In interpreting the term "substantial evidence," FDA has viewed the phrase "adequate and well-controlled investigations, including clinical investigations" as meaning that efficacy determinations must include studies of efficacy in humans.[59]

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[54] FDA's original interpretation was that the plural "clinical investigations" required that the sponsor conduct at least two efficacy studies to support NDA approval. This interpretation was upheld by the courts in Warner-Lambert Co. v. Heckler, 787 F.2d. 147 (3d Cir. 1986). This was changed to at least one efficacy study plus other confirmatory evidence by Section 115 of the Food and Drug Administration Modernization Act of 1997.
[55] 21 C.F.R. § 50.3(c); 21 C.F.R. § 56.102(c); 21 C.F.R. § 314.108(a).
[56] 21 C.F.R. § 314 Subpart I; 64 Fed. Reg. 53,960 (Oct. 5, 1999) (proposed rule); Fed. Reg. 37,988 (May 31, 2002)(final rule).
[57] 21 C.F.R. § 314.600.
[58] 21 C.F.R. § 314.610(a).
[59] 64 Fed. Reg. 53,960 at 53,964 (Oct. 5, 1999).

The Agency went on to state that its original regulations

> did not contemplate situations in which efficacy studies cannot be ethically conducted in humans, and FDA believes that it would be inconsistent with the statute's public health objectives to conclude that FDA cannot use some other basis for considering the efficacy of such products.[60]

The "Animal Rule" regulation as implemented in 2002 is found at 21 C.F.R. § 314 Subpart I.[61]

Thus, public policy requires that FDA may approve drugs in some situations without human trials, despite the apparent statutory requirement for such studies. Applying logic from the rulemaking, FDA would have to conclude that it would be inconsistent with the statute's public health objectives to fail to grant exclusivity in cases where ethical requirements bar human clinical trials.

Further support for the position that FDA takes public health objectives into consideration when interpreting statutory language is found in the grant of exclusivity to drugs approved under the Animal Rule. In addition to approvals where FDA implements public health objectives over statutory and legislative history, FDA also grants three-year exclusivity where the plain language of the statute and the case law suggests that it should not.

Under the terms of FFDCA, a grant of three-year market exclusivity is available for NDAs that seek approval of new intended uses for drug products that contain a previously approved active drug substance. Such exclusivity requires (among other things) that the NDA "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."[62]

Section 505(b)(2) NDAs that lack new clinical investigations data do not receive the exclusivity, since Congress did not see a need to provide the additional incentive for drug

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[60] Id.
[61] 59 Fed. Reg. 50,368 (Oct. 3, 1994).
[62] FFDCA § 505(c)(3)(E).

sponsors that did not incur the effort and expense of a clinical development program. The requirement for new clinical investigations is clear, and (as discussed above) the term clinical investigations has a well-established definition that means human studies. As a result, drugs that contain previously approved active ingredients that are approved under the animal rule should not, by the strict terms of the statute and case law, be eligible for three-year new drug product exclusivity. Nevertheless, FDA has granted exclusivity to such drug products in the past.

For example, FDA approved and granted three-year exclusivity for pyridostigmine bromide as a §505(b)(2) NDA despite the fact that no human clinical data was submitted. The U.S. Army filed an NDA for a nerve gas prophylactic agent that used the previously approved drug ingredient pyridostigmine bromide. The NDA for the drug was approved on the basis of the Animal Rule.[63] Despite there being no human clinical evaluations demonstrating drug efficacy, as required by FFDCA §§ 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii), the drug was granted a three-year exclusivity period. Similarly, NDA 22041 for Cyanokit (hydroxocobalamin) was approved under the Animal Rule, with no human efficacy testing for the approved indication. That NDA was also granted three years of market exclusivity despite a lack of human clinical investigations. The review documents for that NDA clearly state that the application is considered to contain reports of clinical investigations necessary for approval despite the lack of any human clinical trials.[64]

As discussed above, FDA normally requires two well-controlled clinical studies in humans in order to prove that a drug product is safe and effective.[65] In certain cases, FDA has waived this requirement and approved an NDA by finding that a drug product was safe and

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[63] See, Memorandum: Basis of approval of application under the "Animal Efficacy Rule," 21 CFR 314 Subpart I – File NDA 20-414 – use of pyridositigmine bromide (PB) for prophylaxis against the lethal effects of Soman poisoning, Robert Temple, MD, Director Office of Device Evaluation I, February 5, 2003.
[64] Executive Summary, NDA 22041, Cyanokit, November 26, 2006.
[65] FFDCA § 505(d) as historically interpreted by FDA. See, e.g., Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998.

effective based solely on studies in animals. Taking this position to waive human clinical studies was not supported by the FFDCA or any specific Congressional legislation. Instead, FDA recognized that in certain cases it would be unethical to conduct the clinical studies required and that the only way that the drug product can ethically be shown safe and effective would be for the drug product's application to be based solely on animal data. Furthermore, FDA granted three-year exclusivity to these drug products even though the FFDCA specifically requires "clinical studies" in order to support this exclusivity. Therefore, FDA has acknowledged that its highest duty is to ensuring that it does not encourage unethical activity in the private marketplace and that the FDA's positions on the law are flexible enough to ensure that certain drug products can be approved and obtain exclusivity (and thus encourage innovation) even in situations where clinical trials are ethically barred. In the current situation, it would be unethical for Ferring to have conducted clinical trials on the sole ingredient sodium picosulfate without including the other ingredients magnesium oxide and anhydrous citric acid. This is because a single ingredient sodium picosulfate drug product would not have been able to demonstrate effectiveness. As FDA's reviewer stated:

> After examining the literature for evidence of the effectiveness of each component for colon cleansing, the reviewers concluded that a full factorial study could not be conducted due to serious ethical concerns because the literature review indicated that each component as a stand alone would result in inadequate colon cleansing for colonoscopy.[66]

Therefore, Ferring would have to have conducted a clinical trial where the subjects were given a drug whose effectiveness could not ethically be shown in an effort to support the ability to obtain five-year exclusivity.

Because Ferring was ethically barred from conducting a study of single ingredient sodium picosulfate without including the other ingredients magnesium oxide and anhydrous

[66] NDA number 202535 Prepopik™, Division Director Summary Review, Donna Griebel, MD, p 40, July 16, 2012.

citric acid, Ferring could not have obtained a single ingredient NDA for a sodium picosulfate drug product. Therefore, unlike other combination drug products, Ferring was ethically barred from utilizing the single-ingredient NCE NDA to obtain five-year exclusivity to protect its combination drug product.

FDA should treat Ferring's situation similar to those cases where FDA approved a drug product and granted exclusivity based on animal studies. In the Ferring NDA, FDA faces a situation where a drug product will be arbitrarily denied exclusivity due to ethical restraints placed on the possible studies available to the applicant. FDA should again reaffirm that its highest duty is to ensuring that it does not encourage unethical activity in the private marketplace and that it will ensure that certain drug products can be approved and obtain exclusivity even in situations where clinical trials are ethically barred.

V. Conclusion

For the forgoing reasons, Ferring requests FDA amend the exclusivity period granted for Ferring's Prepopik™ drug product under FFDCA §§ 505(c)(3)(E) and 505(j)(5)(F). Ferring also request that the FDA stay acceptance and approval of any ANDA or § 505(b)(2) NDA that references NDA 202535 until the question about the exclusivity period is addressed.

VI. Environmental Impact

A categorical exclusion is claimed in accordance with 21 C.F.R. § 25.30; 21 C.F.R. § 25.31. Therefore, an environmental impact analysis is not required.

VII. Economic Impact

Information on economic impact will be submitted upon request.

VIII. Certification

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: July 17, 2012. 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: Ferring Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition."

Respectfully submitted,

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