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CITIZEN PETITION

The undersigned submits this petition on behalf of Ferring Pharmaceuticals, Inc., the producer of oral desmopressin, in accordance with 21 U.S.C. § 355(j) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. § 10.20, 10.30, 320.32, and 320.33, requesting that the Commissioner of Food and Drugs establish specific bioequivalence requirements for oral products containing desmopressin (also referred to as DDAVP), because of several unique aspects of the drug, including, *inter alia*, (1) it is the first ever and only oral peptide approved by the Food and Drug Administration ("FDA"); (2) its physical-chemical properties as a nonapeptide and very low oral absorption present novel issues with respect to intra-subject as well as inter-subject variations in bioavailability; (3) its very high potency (estimated $EC_{50} < 2$ pg/mL and E_{max} at approximately 4-5 pg/mL)^{1,2,3} and the relative insensitivity of existing assays precludes the use of pharmacokinetic data alone to estimate duration of action, the major determinant of safety; and (4) the non-proportionality of exposure

¹ Hammer M, Vilhardt H, 1985, Peroral treatment of diabetes insipidus with a polypeptide hormone analog desmopressin. J Pharmacol Exp Ther. 1985 Sep;234(3):754-60.

² Callréus T, Odeberg J, Lundin S, Höglund P, 1999, Indirect-response modeling of desmopressin at different levels of hydration. J Pharmacokinet Biopharm. 1999 Oct;27(5):513-29.

³ Internal Ferring Report no: MFFR2001/024/00) (data on file with company).

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(AUC) provided by the two approved strengths, 0.1mg and 0.2mg, indicates non-linear pharmacokinetic properties that necessitate special criteria for establishing bioequivalence . In addition, because desmopressin is primarily indicated for use in enuretic children who may have substantially different pharmacokinetics, pharmacodynamics and other critical variables, data from healthy adults would be insufficient to establish efficacy and safety in the target population. In all these ways, DDAVP differs from other drugs used primarily in children *e.g.*, methylphenidate; and unique criteria must be established in accord with 21 CFR §§ 320.32, 320.33 due to the potential precedent setting ramifications of any generic approval.

A. Action Requested

The Drug Price Competition and Patent Term Restoration Act of 1994 (the “Hatch-Waxman Amendments”) created § 505(j) of the FFDCA, which provides a sponsor with the opportunity to receive FDA approval to market a new generic drug without submitting substantial evidence of the drug product’s safety and effectiveness. Instead, the sponsor may use an Abbreviated New Drug Application (“ANDA”) that relies upon the FDA’s prior finding that the reference listed drug (“RLD”) is safe and provides evidence to show that the ANDA is bioequivalent to the RLD. The statute is based upon the scientific premise that bioequivalent drug products that are the same with respect to everything but formulation (*e.g.*, active ingredient, route of administration, strength, labeling, dosage form, etc.) are bioequivalent, therapeutically equivalent and therefore substitutable under state law. A product is deemed bioequivalent if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the

listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . .⁴

As explained more fully below in Section B, the unusual if not unique properties of orally administered desmopressin call into question the reliability of conventional bioequivalence study procedures and data, mandating that all ANDA sponsors should present additional evidence from appropriately designed studies in children to establish bioequivalence to the RLD. This requirement is especially important for desmopressin because it is the **first ever and only oral peptide** for which a new drug application ("NDA") has been approved and is also the first oral peptide for which ANDAs have been submitted. Of even greater importance, desmopressin is indicated primarily for use by children who constitute a more vulnerable population and also may react to pharmaceuticals in a manner substantially different than adults as Congress and FDA have recognized through enactment of legislation, and rulemaking.⁵ These issues are especially important in the case of desmopressin, which is a potent oral peptide that is available in several dose strengths requiring careful titration in order to optimize the ratio between efficacy and safety.

Therefore, we respectfully request that FDA require ANDAs for products containing desmopressin to address the issues associated with these unique properties of the product, by requiring such ANDAs to include the following:

⁴ 21 U.S.C. § 355(a)(8)(B)(i); 21 C.F.R. § 320.1(e) and 320.23(b).

⁵ Recognition of the differences in pharmacological effects on children compared to adults has been an important theme in both Congressional legislation, and FDA regulation and guidance. This recognition has led to several revisions of the FDCA since 1997 concerning pediatric studies for new drugs, including: Food and Drug Administration Modernization Act of 1997, Public Law 105-115, § 111; Best Pharmaceuticals for Children Act, Public Law No. 107-109; Pediatric Research Equity Act of 2003, Public Law 108-155. FDA regulations have recognized the importance of separate pediatric data for drugs since 1994, when it amended its regulations to provide for specific labeling of pediatric information, 21 C.F.R. § 201.57(f)(9).

- (1) Evidence from appropriately designed comparative clinical studies demonstrating bioequivalence to desmopressin in terms of both pharmacokinetic and pharmacodynamic properties including intrasubject as well as intersubject variability in adsorption **and** duration of action as determined by measurement of urine osmolarity and flow rates in water loaded enuretic children.
- (2) Separate bioequivalence evidence for each dose level, due to the lack of dose proportionality between strengths in the RLD.
- (3) If bioequivalence is not established by the above specified pharmacokinetic and pharmacodynamic studies in enuretic children, ANDAs for products containing desmopressin must provide evidence from appropriately designed and validated comparative clinical trials demonstrating efficacy and safety equivalent to RLD in this target population.

B. Statement of grounds

I. Introduction

Desmopressin formulated as an oral tablet is indicated for: (1) the treatment of primary nocturnal enuresis in children 6 years of age or older; and (2) the treatment of central diabetes insipidus in children 4 years of age and older. Aventis owns the NDA and has been granted exclusive United States marketing rights by Ferring Pharmaceuticals. The NDA was the first submitted for approval of an oral dosage form for any peptide intended for absorption and systemic action.⁶ The latest patent on oral administration of desmopressin is not due to expire

⁶ See Comments of Gloria Troendle, Group Leader, August 9, 1993, DDAVP Tablets Summary Basis of Approval,

until December 23, 2013. An ANDA with a paragraph 4 certification has been submitted for the oral formulation. There may be other ANDAs filed or soon to be filed. As far as we are aware, this is the first submission of an ANDA seeking approval of an oral peptide.

The uniqueness of this ANDA is vital to recognize because it will likely establish precedents for other oral peptides in the future. The efficacy and safety of oral desmopressin therapy for PNE in children depends critically upon several parameters that are not adequately assessed by conventional tests of bioequivalence in healthy adults. The most critical deficiencies are a lack of information about (1) the total *duration of antidiuretic action* which determines the risk of hyponatraemia; (2) night to night (intra-subject) variability in the rate, extent and duration of absorption which determine the overall efficacy as well as safety of the treatment and (3) the impact of age and development on these pharmacodynamic and pharmacokinetic parameters.

Due to desmopressin's physico-chemical properties (a nonapeptide with a molecular weight of approximately 1069), its bioavailability when given orally tends to be very low (approximately 0.16 %) and to vary significantly not only from subject to subject but also from day to day in the same subject (CV% =104 of AUC after administration of 200 µg).⁷ The magnitude of this variation determines the extent of day to day differences in efficacy (the level of antidiuretic action during the first 8 to 10 hours) as well as safety (the duration of antidiuretic action after the first 8 to 10 hours). They depend in part on the extent to which the release of desmopressin from inert ingredients in the formulation may be altered by food, pH and other unknown and/or uncontrolled variables in the GI tract. Thus, single dose bioavailability/bioequivalence studies would not necessarily predict repeated dose pharmacokinetics or overall efficacy or safety as absorption would vary from time to time.

NDA 19-955.

⁷ Internal NDA data RG 84063-102.

Consequently, the minimum requirement for equating the overall efficacy and safety of a generic formulation to RLD should be to demonstrate equivalent, day to day intra-subject variation at an equally effective dose in the target population. Failing this, a full scale clinical trial of the generic formulation would be necessary to establish overall efficacy and safety comparable to RLD.

The inability of conventional bioequivalence studies to adequately assess the duration of antidiuretic action of desmopressin is due to the unusual potency of the peptide and the inability of current assays to consistently detect the drug in plasma at concentrations that continue to exert a significant antidiuretic effect. Hammer and Vilhardt examined the pharmacodynamic effect of desmopressin in nine diabetes insipidus patients. It was found that the maximal effect of desmopressin on water permeability of the collecting ducts was reached at plasma levels of 4 to 5 pg/mL.⁸ Callréus developed an indirect-response PK/PD model of desmopressin, based on data from eight water loaded healthy subjects. The results of this analysis showed an IC₅₀ value of 3.7pg/mL.⁹ As the indirect response model of the PK/PD relation was found to be very steep (Hill factor of 13), the maximal effect would be in a similar range (about 5 pg/mL) as discussed in the above cited publication by Hammer and Villardt. PK/PD modeling of data from studies in healthy volunteers as well as patients with nocturia has shown that the EC₅₀ with respect to antidiuretic activity (urinary output) is approximately 1-2 pg/mL.¹⁰ This confirms the published low plasma levels of desmopressin at which clinical effect can be expected - below the LLOQ for most bioanalytical methods. Because of this assay limitation and the possibility that some formulations result in prolonged gastrointestinal absorption in undetectable but still biologically active amounts of the drug, the true duration of action may be grossly underestimated by PK data alone. It can be determined accurately only by pharmacodynamic studies (i.e. measurements of

⁸ Hammer, Vilhardt, supra.

⁹ Callréus et al., supra.

¹⁰ Internal Ferring Report no: MFFR2001/024/00 (data on file with company).

urine osmolarity and flow) in subjects who have been water loaded to suppress interference by endogenous antidiuretic hormone, arginine vasopressin. Underestimating the true duration of action of a new formulation of desmopressin also underestimates the risk of hyponatraemia because the latter is caused by excessive retention of water that results when the period of drug induced antidiuresis is prolonged sufficiently to prevent a full, compensatory water diuresis before the next dose is taken the following night. Thus, the minimum requirement for equating the safety of a generic formulation to RLD in children should be to show an equivalent duration of action *at an equally effective dose* by appropriate pharmacodynamic studies in subjects water loaded to suppress interference from endogenous vasopressin. Failing this, a full scale clinical trial of the generic formulation would be necessary to establish safety comparable to RLD.

In addition to these unusual properties, the two approved strengths of desmopressin tablets (0.1 mg. and 0.2 mg.) do not give proportionally similar drug exposure. The AUC and C_{max} values were not proportional between 0.1 and 0.2 mg dose levels.¹¹ This finding was reinforced by studies found in the original NDA, including, for example, Study RG-84063-102 conducted by Dr. Thomas Hunt of Pharmaco Dynamics Research, Inc., the study concluded that the 0.1 mg. and 0.2 mg. doses were not bioequivalent, and that a single 0.2 mg. tablet produced greater total systemic absorption of DDAVP than did two 0.1 mg. tablets. This difference may be due at least in part to differences in the proportion of active and inactive ingredients in the two tablets. Although the lower dose contains 50% of the amount of active ingredient, it does not contain 50% of every inactive ingredient that the higher dose contains¹² and the inactive ingredients contained in the 0.1 mg. dose are not precisely one-half of the quantity contained in the 0.2 mg dose. Thus, pharmacokinetic and pharmacodynamic data from trials using the 0.2

¹¹ Ferring Report. Study RG84063-101.

¹² See U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry: BA and BE Studies for Orally Administered Drug Products – General Considerations.

mg. dose cannot be extrapolated to the 0.1 mg. dose (or vice-versa) and separate studies must be conducted at each dose level.

Finally, it should be noted that the principal indication for desmopressin therapy is enuretic children and children generally have different pharmacokinetics and metabolism than adults.¹³ In addition, a difference in GI absorption between children and adults may vary depending on the formulation, and enuresis may be associated with a diminished nocturnal renal sensitivity to the antidiuretic effects of the drug.¹⁴ No exposure-response relationship has been established for children with Primary Nocturnal Enuresis. The problem is further magnified in the case of DDAVP, since it must be carefully titrated in order to achieve the appropriate balance between efficacy and safety. According to the approved labeling, the dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. An ANDA claiming to be bioequivalent with DDAVP solely on the basis of pharmacokinetics and pharmacodynamic data from adult healthy volunteers may not be bioequivalent in children. Thus, children that are currently well treated with DDAVP may, after a therapy change to an ANDA-product, experience decreased efficacy or increased side effects due to different pharmacokinetic properties. Therefore, it is of utmost importance that clinical bioequivalence studies for any ANDA are conducted in enuretic children, to minimize any changes in efficacy or safety risk that may result from replacing DDAVP with an ANDA.

The ramifications to the review of ANDAs are far-reaching and will impact the tens of thousands of children and others who depend upon DDAVP because they may be motivated or required to purchase possibly inequivalent generic products if they become available. FDA must

¹³ Jungbluth GL, Welshman IR, Hopkins NK., Linezolid pharmacokinetics in pediatric patients: an overview. *Pediatr Infect Dis J.* 2003 Sep;22(9):S153-S157.

¹⁴ Robertson GL, Rittig S, Kovacs L, Gaskill MB, Zee P, Nanninga J. Pathophysiology and treatment of enuresis in adults. *Scand J Urol Nephrol* 33: Suppl 202: 36-39, 1999.

ensure that such generic products are equally as safe and effective. Because the issues associated with these ANDAs are novel and unprecedented, and the ramifications of the agency's decisions will be significant, FDA should proceed cautiously.

II. To establish bioequivalence the ANDA sponsor must submit evidence from appropriately designed bioequivalence studies in the target population

Section 505(j) of the FDCA permits a company to apply for a license to market a drug through the submission of an ANDA. FDA can approve an ANDA only upon a showing that the generic drug is "the same" as RLD with respect to its active ingredient(s), dosage form, bioavailability, route of administration, and intended use.¹⁵ If the ANDA sponsor cannot establish that the products are therapeutically equivalent, through conventional bioavailability studies, the company must submit an application containing substantial evidence that the product is safe and effective for its intended use as proof of bioequivalence. In general, this means providing data from at least one adequate and well-controlled clinical trial demonstrating that the product is as safe and effective for its intended use as the RLD.

In most cases, the key issue in establishing that a generic product is "the same" concerns bioavailability through conventional blood level studies in adults. FDA requires the ANDA to contain data establishing that the product is "bioequivalent" to the reference listed drug, meaning the following:

the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents¹⁶ or pharmaceutical alternatives¹⁷ becomes available at

¹⁵ 21 U.S.C. § 355(j).

¹⁶ Pharmaceutical equivalents are drug products that contain identical amounts of the identical active ingredient in the identical dosage form. 21 C.F.R. § 320.1(c).

¹⁷ Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but

the site of drug action when administered at the same molar dose
under similar conditions in an appropriately designed study. . . .¹⁸

The type of evidence that FDA will accept as sufficient for establishing bioequivalence varies. In some rare instances, *e.g.*, intravenous solutions, only *in vitro* studies are required. Most other circumstances require an *in vivo* test in humans in which the concentration of the active moiety in whole blood, plasma, serum or other biological fluid is measured as a function of time. But FDA's regulations list a hierarchy of testing that can be used to establish bioequivalence. In the case of desmopressin, the drug's properties, formulations, and usage mandate that bioequivalence be established only through appropriately designed comparative studies in children to ensure that the drug products will be safe and effective under the primary conditions of actual use and labeling.

C.F.R. § 320.24(b) identifies the *in vivo* and *in vitro* approaches for determining bioequivalence. Because of the characteristics of oral desmopressin, comparative clinical trials probably would provide the surest measure of equivalent efficacy and safety. As a minimum, however, expanded PK and PD studies as outlined above are required and might be acceptable for reasonable assurance of equivalent efficacy and safety, even though the biomarkers urinary osmolality and output have not been prospectively validated against clinical endpoints (dryness) in the PNE population. Traditional bioequivalence studies relying solely on bioanalytical assays cannot provide assurance of safety and efficacy. Pharmacokinetic as well as pharmacodynamic (*e.g.* urinary osmolality and urinary output) measurements would be necessary in the target population to meet FDA requirements that protect public health. Generally, pharmacodynamic studies are not recommended for orally administered drug products when the drug is absorbed

not necessarily in the same amount or dosage form or as the same salt or ester. 21 C.F.R. § 320.1(d).

¹⁸ 21 C.F.R. § 320.1(e).

into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish bioequivalence. However, in those instances where a pharmacokinetic approach is not possible (or adequate, as for DDAVP), suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.¹⁹ The findings of extensive research conducted over the last 15 years indicate that nocturnal enuresis in children has a multifactorial aetiology.²⁰ Indeed, it has been proposed that the disorder should be regarded as a group of different conditions with different aetiologies. This is reflected in the modern classification, which divides nocturnal enuresis into several subgroups according to history, symptoms and therapeutic response.²¹ In all papers dealing with therapy in nocturnal enuresis the endpoint has been reduction in number of wet nights and despite many studies and hypotheses there is yet no clear understanding about the mechanism of action of the different therapies.²² There is no established correlation between an increase in urine osmolality and clinical response to desmopressin in PNE and it has never been shown that a decrease in urine production leads to dryness (clinical effect). Nevertheless, it is not unreasonable to presume that such a correlation exists since antidiuresis is the only recognized significant physiologic effect of desmopressin and any other mechanism of action would probably also depend on blood levels of the drug. Therefore, our proposed alternative to expand pharmacokinetic and pharmacodynamic studies probably would provide an acceptable though imperfect surrogate for full scale, comparative clinical trials to establish equivalent efficacy and safety of generic formulations. There are, however, legitimate reasons to suppose that even expanded pharmacokinetic and

¹⁹ Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003.

²⁰ Nørgaard JP, Djurhuus JC, Watanabe H, Stenberg A, Lettgen B, Experience and current status of research into the pathophysiology of nocturnal enuresis. *British Journal of Urology* 1997; 79; 825 – 835.

²¹ Djurhuus JC, Definitions of Subtypes of Enuresis. *Scandinavian Journal of Urology and Nephrology*. 1999; vol 33; suppl 202; 5 – 7.

²² Läckgren G, Hjälmsås K, van Gool J, von Gontard A, de Gennara M, Lottmann H, Terho P, Nocturnal enuresis: A suggestion for a European treatment strategy. *Acta Pædiatrica* 1999; 88: 679 – 90).

pharmacodynamic studies in children may not be sufficient to establish efficacy equivalence to the RLD, and that comparative clinical studies may be necessary.

There is no *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability data. Similarly, there is no *in vivo* test in animals that has been correlated with and is predictive of human bioavailability data.²³

The problems presented by desmopressin and, more specifically, its large molecular weight, are clearly reflected in FDA regulations. 21 C.F.R. § 320.33 lists several factors that FDA is to consider in identifying specific pharmaceutical equivalents that are not, or may not be, bioequivalent. Almost all apply to desmopressin. For example, there has been a competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition.²⁴ In addition, the particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability, as discussed above.²⁵ Certain physical structural characteristics of the active drug ingredient (e.g., polymorphic forms, conformers, solvates, complexes, and crystal modifications) dissolve poorly, and this poor dissolution affects absorption. There is also a high ratio of excipients to active ingredients (greater than 5 to 1), and specific inactive ingredients (e.g., hydrophilic or hydrophobic excipients and lubricants) either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with such absorption.²⁷

²³ 21 C.F.R. § 320.24(b)(1)(ii) and (iii).

²⁴ 21 C.F.R. § 320.33(d). See statement of Dr. Gary Robertson.

²⁵ 21 C.F.R. § 320.33(e)(3). See Gloria Troendle's statement.

²⁷ 21 C.F.R. § 320.33(e)(4), (5) and (6).

Desmopressin undergoes luminal degradation in the gut, which in addition to its molecular weight and physical chemical properties reduces the oral bioavailability: The degree of absorption of the active ingredient is poor (the absolute bioavailability is approximately 0.16%), even when administered in pure form (*e.g.*, solution).²⁸ The drug product is subject to dose dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence.²⁹ Further, the ratio of excipients to active ingredient is an extraordinarily high 100 - 200 to 1.

FDA has historically recognized that such drug products present bio-problems. For those drug products, more data are necessary to establish bioavailability and bioequivalence, through conventional bioavailability studies (*i.e.*, fed, fasting, and steady state). In extreme cases, FDA can require a unique bioequivalence standard. At a minimum, DDAVP is such a drug, not only because of its known bioavailability problems, but also because of the careful dose titration that is required. The labeling recommends beginning patients on doses of 0.05 mg two times a day and individually adjusting it to the optimum therapeutic dose, measured by adequate water turnover and sleep. We know that there is the potential for water intoxication and hyponatremia. In addition, it is well known that desmopressin in high doses releases clotting factors von Willebrand Factor and Factor VIII. If bioavailability differs in a material way, safety issues could arise or effectiveness could diminish. Clearly, given the circumstances, establishing safety and efficacy based on blood levels alone are problematic.

FDA is aware of the concerns associated with the absorption, and equivalence, of peptides. The agency has encountered them before, for example, in the context of calcitonin. The agency has struggled to develop a uniform approach, and has addressed the issue on an

²⁸ 21 C.F.R. § 320.34(f)(2).

²⁹ 21 C.F.R. § 320.34(f)(6).

individualized, company by company basis. A unilateral approach for showing bioequivalence of two drug products containing this peptide benefits no one. A public process is necessary for valid, comprehensive scientific resolution of the issues in a way that will provide safe, effective reasonably priced drug products.

The agency has demonstrated caution in reviewing products that present novel issues of bioavailability and it has been inclined to require clinical studies, for example, the establishment of guidelines for metered dose inhalers (“MDIs”). FDA recognized that MDIs have unique differences that (among other things) render the concept of classical bioequivalence and bioavailability inapplicable. FDA noted that because of the typically small dose, blood concentrations are generally undetectable. Moreover, only 10-15% of the dose reaches the biological target. Because the remainder of the dose is trapped in the mouth and pharynx, and is swallowed and absorbed through the gastrointestinal tract, additional studies would be necessary even if it were possible to measure blood concentration. For these reasons, FDA requires clinical approaches to measuring bioavailability and establishing bioequivalence.³⁰ This complexity led Congress to create a new statutory standard that permits alternative methods specifically intended to deal with the issue for drug products that are not intended to be absorbed into the blood stream.³¹

These concerns are similar to a problem noted by Gloria Troendle, the group leader responsible for the review of DDAVP. Ms. Troendle noted the difficulty of demonstrating

³⁰ FDA, CDER Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products: Chemistry, Manufacturing and Controls Documentation, at 3 (1998).

³¹ Medicare Prescription Drug Improvement and Modernization Act of 2003 (Public Law 106-554), § 1103 (amends FFDCA § 505(j)).

absorption of the drug product, because only a “very small fraction” (0.7 to 1%) of the drug dose is expected to be absorbed.³²

The reasons set forth herein justify similar evaluation of desmopressin products. As the first and only approved oral peptide that presents complex and novel bioavailability issues, FDA should carefully consider these issues in its review. The fact that this product is primarily indicated for use in children presents an additional complicating factor, and highlights the importance in taking a judicious approach. For all these reasons, bioequivalence trials in the target pediatric population demonstrating pharmacokinetic and pharmacodynamic equivalence (after single as well as repeated dosing) between the test product and the reference (DDAVP) product is the minimum necessary to establish their bioequivalence in accord with FDA's regulations, precedent, and sound science.

III. Evidence that the product is safe and effective in children is necessary, since the product is primarily indicated for use by children, and the pharmacokinetics of children are generally recognized to be substantially different.

As the indication suggests and the actual use of the product shows, DDAVP primarily is for use in children for nocturnal enuresis. It is undisputed that the metabolism, pharmacokinetic, and pharmacodynamics of drugs in children can be substantially different than in adults, as the United States Congress recognized in enacting the Best Pharmaceuticals for Children Act of 2001, and FDA independently verified in its rulemaking procedure.³³ Congress enacted this statute in order to promote the study of drug products in children. Recognition of this need represents an acknowledgment that one cannot routinely prescribe a drug product for a child simply by approximating a titration of a dose that was studied only in adults. It is well-recognized

³² See, *supra*, note 2.

³³ See Pub. L. No. 107-109; 115 Stat. 1408 (2002).

that children absorb, metabolize, distribute and excrete drugs differently than adults. Without data establishing that these factors are proportional between adults and children, as was done for the small molecule methylphenidate, these factors must be studied. Because DDAVP is primarily used in children, the pharmacokinetics and pharmacodynamics of any generic desmopressin product must be studied in children as well because of the absence of data resolving this issue.³⁴

This concept is further reflected in agency regulations and guidance documents. The guidance document entitled "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products" explicitly recognizes that the pharmacokinetics of persons under the age of sixteen years old are expected to be different.³⁵ This is especially true of drugs with complex pharmacokinetic properties that prevent the extrapolation of adult data to pediatric patients.³⁶ All of these facts are true of desmopressin, due to its unique properties discussed above and the special absorption problems those properties cause, as shown in Part II above. Even in adults, there are issues with product absorption. The additional factor of the product's primary use in children further complicates the matter, and provides additional reason to proceed cautiously and require special study in children.

V. Conclusion

DDAVP is the first and only oral peptide drug product approved for use. It is intended and used primarily for treatment of nocturnal enuresis in children. The unique properties and

³⁴ See statement of Dr. Gary Robertson.

³⁵ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry - General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products, at page 2.

³⁶ Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biologics in pediatric patients; final rule. 63 Fed. Reg. 66631, 66644 (1998).

uses of the drug necessitate expanded pharmacokinetic and pharmacodynamic studies if not full scale clinical trials to establish that any generic formulation is equivalent to RLD in bioavailability in enuretic children in accord with FDA's applicable regulations. Imposing this requirement is consistent with the Agency's traditional method of dealing with unique, precedent setting drug products.

D. Environmental Impact

In accordance with 21 C.F.R. § 25.31(c), an environmental impact analysis is not required.

E. Certification

The undersigned certified, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

A handwritten signature in black ink, appearing to read "Edward John Allera", is written over a horizontal line.

Edward John Allera
Counsel to Ferring Pharmaceuticals, Inc.
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List of Attachments

1. Gary L. Robertson, Statement of expert opinion in support of the Buchanan Ingersoll Citizen Petition regarding generic desmopressin.
2. Hammer M, Vilhardt H, 1985, Peroral treatment of diabetes insipidus with a polypeptide hormone analog desmopressin. *J Pharmacol Exp Ther.* 1985 Sep;234(3):754-60.
3. Callréus T, Odeberg J, Lundin S, Höglund P, 1999, Indirect-response modeling of desmopressin at different levels of hydration. *J Pharmacokinet Biopharm.* 1999 Oct;27(5):513-29.
4. Jungbluth GL, Welshman IR, Hopkins NK., Linezolid pharmacokinetics in pediatric patients: an overview. *Pediatr Infect Dis J.* 2003 Sep;22(9):S153-S157.
5. Robertson GL, Rittig S, Kovacs L, Gaskill MB, Zee P, Nanninga J. Pathophysiology and treatment of enuresis in adults. *Scand J Urol Nephrol* 33: Suppl 202: 36-39, 1999.
6. Nørgaard JP, Djurhuus JC, Watanabe H, Stenberg A, Lettgen B, Experience and current status of research into the pathophysiology of nocturnal enuresis. *British Journal of Urology* 1997; 79; 825 – 835.
7. Djurhuus JC, Definitions of Subtypes of Enuresis. *Scandinavian Journal of Urology and Nephrology.* 1999; vol 33; suppl 202; 5 – 7.
8. Läckgren G, Hjälms K, van Gool J, von Gontard A, de Gennara M, Lottmann H, Terho P, Nocturnal enuresis: A suggestion for a European treatment strategy. *Acta Pædiatrica* 1999; 88: 679 – 90).
9. Comments of Gloria Troendle, Group Leader, August 9, 1993, DDAVP Tablets Summary Basis of Approval, NDA 19-955.