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Food and Drug Administration
Rockville MD 20857

Edward John Allera
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1776 K Street, N.W.
Washington, D.C. 20006

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Re: Docket No. 2004P-0068/CP1

Dear Mr. Allera:

This letter responds to your citizen petition dated February 2, 2004 (Petition) and your related supplement dated April 19, 2005 (Supplement), both on behalf of Ferring Pharmaceuticals, Inc. (Ferring).¹ The Petition requests that the Food and Drug Administration (FDA or the Agency) establish certain bioequivalence (BE) requirements for generic oral desmopressin products that are submitted for approval in abbreviated new drug applications (ANDAs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act).² Specifically, you request that FDA require ANDAs for such products to include the following:

- Evidence from appropriately designed comparative clinical studies demonstrating BE to the reference listed drug (RLD),³ Aventis' DDAVP tablets (desmopressin acetate, 0.1 mg and 0.2 mg) (DDAVP), in terms of both pharmacokinetic and pharmacodynamic properties, including intra-subject as well as inter-subject variability in absorption and duration of action as determined by measurement of urine osmolarity and flow rates in water-loaded enuretic children;
- If BE is not established by the pharmacokinetic and pharmacodynamic studies above, evidence from appropriately designed and validated comparative clinical trials demonstrating efficacy and safety equivalent to the RLD in enuretic children; and
- Separate BE evidence for each dose level.

¹ In responding to the Petition, we have also considered the comments submitted by Christine J. Siwik of Rakoczy Molino Mazzochi Siwik LLP on behalf of Barr Laboratories, Inc., to the Petition docket (2004P-0068/CP1). We note that, in the Supplement, you advised that you anticipated submitting additional comments within two weeks of the Supplement's submission. More than two months have passed since the date of the Supplement, and we have received no further comments from you as of this writing.

² Although the term "generic" is not defined in the Act or FDA's regulations, it is used in this letter to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act. The phrase "generic oral desmopressin products" is used to describe the oral desmopressin products with which your petition is concerned (i.e., those subject to section 505(j) of the Act that reference the approved drug desmopressin acetate.

³ A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 CFR 314.3. RLDs are identified in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

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As explained below, the reliability and the relative merits of methodologies to assess BE are well established. Essentially, you request that, in the case of desmopressin, the Agency augment and modify the generally preferred methodology for determining BE for oral dosage form products.⁴ However, you offer no convincing evidence (i.e., data or other information) that any of your proposed changes are needed. Accordingly, not having been presented with any basis for departing from our long-established and well-settled practice, we deny your petition in its entirety.

I. BIOEQUIVALENCE IN BRIEF

A drug product such as desmopressin that is systemically absorbed is bioequivalent to another if:

[T]he 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

⁵
....

The rate and extent to which a drug product's active ingredient or active moiety is absorbed and becomes available at the site of action in the body is defined as the drug's bioavailability (BA).⁶

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman or the Hatch-Waxman Amendments) created section 505(j) of the Act, which describes the current approval process for ANDAs and the central role of BE testing in it.⁷ The showing that must be made for an ANDA to be approved is different from that which is required in a new drug application (NDA). An NDA applicant must show that the drug product is safe and effective, generally through data and information derived from clinical and pre-clinical trials.⁸ In contrast, if an ANDA applicant can demonstrate that its generic drug product is the same as the RLD in certain respects (e.g., active ingredient,

⁴ As discussed below, the preferred methodology if available (and if a waiver is not appropriate) is an in vivo test in healthy adults in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time.

⁵ Section 505(j)(8)(B)(i) of the Act; see also 21 CFR 320.23(b). As 21 CFR 320.1(e) explains, BE is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." As noted later in this response, courts have upheld FDA's discretion to determine how the statutory requirement for demonstrating BE is satisfied.

⁶ See Section 505(j)(8)(A)(i) of the Act and 21 CFR 320.1(a).

⁷ Section 505(j) was recently amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 in ways not relevant to the Petition.

⁸ See sections 505(b) and (c) of the Act.

dosage form, route of administration), and is bioequivalent to the RLD, the statute permits an ANDA to rely on FDA's previous finding that the RLD is safe and effective.⁹

FDA has the discretion to determine what type of information is necessary to satisfy the statutory requirement for BE.¹⁰ FDA regulations at 21 CFR part 320 establish acceptable methodologies for determining the bioequivalence of drug products. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies. The regulations list the various methodologies in order of accuracy, sensitivity, and reproducibility (21 CFR 320.24). Applicants must use the most accurate, sensitive, and reproducible method available (21 CFR 320.24(a)).

In descending order of accuracy, sensitivity, and reproducibility, the methods for establishing BE include:

- An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time;
- An in vitro test that has been correlated with and is predictive of human in vivo BA data;
- An in vivo test in humans in which the urinary excretion of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), is measured as a function of time;
- An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility; and
- Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring BA, or appropriately designed comparative clinical trials, for purposes of demonstrating BE.

⁹ See section 505(j)(2)(A)(iv) of the Act. As discussed in the Orange Book, if, in addition to being bioequivalent, two drug products (e.g., a generic drug product and its RLD) (1) are approved as safe and effective, (2) are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity, (3) are adequately labeled, and (4) are manufactured in compliance with Current Good Manufacturing Practice regulations, they will be classified as therapeutically equivalent. A therapeutically equivalent drug product "can be expected to give the same therapeutic effect" as the RLD for each of the RLD's approved indications. *Therapeutically Equivalent Drugs, Availability of List*, 45 Fed. Reg. 72582, 72583 (October 31, 1980). Note that an applicant may submit a suitability petition seeking permission to submit an ANDA for a drug product that differs from the RLD in certain respects and, therefore, is not therapeutically equivalent to it. See section 505(j)(2)(C) of the Act and 21 CFR 314.93.

¹⁰ See *Schering Corp. v. FDA*, 51 F.3d 390 at 399 (3rd Cir. 1995) ("Although the Act mandates a showing of bioequivalence for generic drug approvals, there is no evidence that Congress intended to limit the discretion of FDA in determining when drugs were bioequivalent for purposes of ANDA approval").

In addition, Agency regulations articulate basic principles and specific requirements for BA and BE testing. For example, the regulations articulate the principle of avoiding unnecessary human testing¹¹ and call for studies generally to be single-dose studies conducted in healthy adults.¹² The courts have expressly upheld FDA's regulatory implementation of the Act's BE requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

Opinions of medical experts substantiated through many years of regulatory experience continue to reaffirm the soundness of the principles, standards, and methodological rankings set forth in the Agency's regulations and under which we operate to assess BE. This is not to say that the Agency does not take into account new information in assessing the reliability of BE testing for a particular drug product. The Agency will take into consideration persuasive new information submitted in a petition or otherwise. As explained in the preamble to our 1992 final ANDA regulations, "It is highly unlikely that a clinically significant difference in product safety and efficacy will exist for a product that meets an applicable bioequivalence standard. However, should postmarketing surveillance or other information suggest the possibility of therapeutic inequivalence, the approval criteria for that drug entity would be reevaluated."¹³

II. BACKGROUND ON DESMOPRESSIN AND DDAVP

Desmopressin is the active moiety in DDAVP. DDAVP is the first and, to date, only approved oral desmopressin drug product. As you note, Aventis owns the approved NDA for DDAVP (NDA 19-955); you further state that Ferring produces oral desmopressin and has granted Aventis exclusive marketing rights for this substance (Petition at 1 and 4 to 5).

Desmopressin acetate is a synthetic analogue of the pituitary hormone 8-arginine vasopressin, which is an antidiuretic hormone affecting renal water conservation. DDAVP has a molecular weight of 1183.34 daltons and an empirical formula of $C_{43}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$. Following oral administration, DDAVP undergoes extensive enzymatic degradation in the gastrointestinal tract. A sufficient amount of the active moiety (desmopressin) is, however, absorbed to produce a pharmacological response. The onset of antidiuretic response occurs about one hour after DDAVP's oral administration, while the drug's maximum effect, as determined by the measurement of increased urine osmolality, is achieved around four to seven hours after administration.

DDAVP is approved for the following indications: (1) as an antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of temporary polyuria (excessive urination) and polydipsia (excessive thirst) following head

¹¹ See 21 CFR 320.25, which states that, "The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done."

¹² See 21 CFR 320.25(a)(2) and 320.26(a).

¹³ *Abbreviated New Drug Application Regulations*; Final Rule, 57 FR 17950, 17977 (April 28, 1992).

trauma or surgery in the pituitary region, and (2) for the management of primary nocturnal enuresis, when used either alone or as an adjunct to behavioral conditioning or other nonpharmacologic intervention.

At this time, any ANDA for a generic oral desmopressin product would be required to reference DDAVP as its RLD. As you note, at least one ANDA referencing DDAVP has been submitted to FDA with a paragraph IV certification.¹⁴ Because desmopressin can be accurately detected and measured in plasma over time, a generic oral desmopressin product's BE to DDAVP can be established by the most sensitive, accurate, and reproducible method for demonstrating BE described in our regulations, i.e., an in vivo test in humans in which the concentration of the active moiety (desmopressin) in plasma is measured as a function of time.¹⁵ This method is described herein as conventional or pharmacokinetic BE testing.

III. DISCUSSION

A. **The Petition's Request that ANDAs for Generic Oral Desmopressin Products Be Required to Contain Specific Clinical Data Is Not Warranted**

In support of your request that FDA require ANDAs for generic oral desmopressin products to include (in addition to pharmacokinetic BE testing) comparative clinical data documenting equivalence to the RLD in terms of drug pharmacodynamics or, in the alternative, comparative clinical safety and efficacy data, the Petition asserts that conventional BE testing does not provide information about the following: (1) variations within the same individual, day to day (intra-subject variability), in the rate, extent, and duration of drug absorption,¹⁶ (2) the total duration of a product's antidiuretic action, and (3) the impact of an individual's age and development (child versus adult) on these parameters (Petition at 5). You maintain that these factors are critical in determining the safety and efficacy of a desmopressin product (Petition at 5 to 6).

¹⁴ This certification, described at 21 CFR 314.94(a)(12)(i)(A)(4), states that the patent subject to the certification is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted.

¹⁵ See 21 CFR 320.24(b)(1)(i).

¹⁶ In addition to requesting assessment of intra-subject variability relative to the RLD, we note that, as previously mentioned, the Petition requests that we require ANDA applicants to conduct pharmacodynamic or well-controlled clinical studies to demonstrate equivalent inter-subject variability. Conventional BE studies, through their crossover design, employ subjects as their own controls to minimize the potential for study results to be influenced by inter-subject variability. Other than making the request, the Petition and Supplement make no further mention of the issue or argument for why conventional BE studies do not adequately account for inter-subject variability, and do not provide any scientific substantiation of the need for pharmacodynamic or clinical studies, in addition to conventional BE studies, to address such variability. We are not aware of any reason to conclude that conventional BE studies would not adequately account for inter-subject variability in subjects administered desmopressin. Accordingly, we consider this request no further.

You do not provide any evidence that any of this additional data or information is needed to demonstrate BE, however, or that conventional BE testing is not adequate to establish the BE of generic oral desmopressin products to the RLD; nor are we aware of any evidence to support your assertions. Therefore, we do not agree that the comparative clinical studies you request must be provided in ANDAs for generic oral desmopressin products.

1. The Petition Misunderstands the Role of BE Studies and Established Methods for Assessing BE

BE studies are not intended, nor are they appropriate, to measure the factors the Petition identifies. Rather, as explained above, the purpose of BE studies is to determine whether a significant difference exists between the rate or extent of bodily absorption of the active moiety from a drug product proposed in an ANDA and the rate or extent of bodily absorption of the active moiety from the RLD.

You request that we require applicants seeking approval of ANDAs for generic oral desmopressin products to submit pharmacodynamic and/or comparative clinical data to demonstrate BE, in addition to submitting conventional BE testing. However, as our regulations reflect, in the case of products like oral desmopressin that are intended for systemic distribution within the body, and for which drug concentration levels can be measured in blood plasma, the additional data you request would be expected to be *inferior* to the measurement of plasma drug levels for establishing BE.¹⁷ You fail to present (nor have we otherwise seen) evidence either to refute this conclusion as to the additional data's inferiority, to demonstrate that conventional BE testing is inadequate, or to show that its augmentation by the additional data would enable more accurate determination of BE for generic oral desmopressin products than would conventional testing alone.

Notably, the Petition also fails to disclose or describe a published study conducted by Aventis, the sponsor of the DDAVP NDA, on various desmopressin formulations that appears inconsistent with your position that pharmacodynamic or other clinical studies

¹⁷ See 21 CFR 320.24(b). Your petition itself seems to acknowledge the imprecision associated with reliance on pharmacodynamic or clinical endpoints; as you state, “[T]here is yet no clear understanding about the mechanism of action [of desmopressin]. There is no established correlation between an increase in urine osmolality [a pharmacodynamic endpoint for which you request that we establish a specific data requirement] and clinical response to desmopressin in PNE [primary nocturnal enuresis] and it has never been shown that a decrease in urine production leads to dryness (clinical effect)” (Petition at 11).

are needed to establish the BE of oral desmopressin products (as discussed below, this study also appears inconsistent with your position in other respects).¹⁸ The Petition, in fact, does not cite any studies unfavorable to your arguments.¹⁹ Accordingly, we find your request for additional data unjustified.

2. Multiple-Dose Studies Are Not Needed to Address Intra-Subject Variability for Desmopressin

You contend that because of desmopressin's low and variable BA, single-dose BE studies do not adequately predict a generic oral desmopressin product's multiple-dose pharmacokinetics or its overall safety or efficacy (Petition at 5). You submit that desmopressin's BA may be altered by food, pH, and other variables in the gastrointestinal tract, and conclude that clinical data are needed to demonstrate equivalent intra-subject variability between a generic oral desmopressin product and its RLD, DDAVP (Petition at 5 to 6). Again, your arguments reflect a misunderstanding of the standards for approval of an ANDA.

ANDA applicants for generic oral desmopressin products are not required to determine the products' multiple-dose pharmacokinetics to establish BE. As previously discussed, the Act directs that the purpose of a BE study is to detect significant differences between the rate and extent of absorption of the active ingredients or active moieties from two drug products. In general, and as reflected in our regulations, this is best accomplished through a single-dose study.²⁰ As our guidance on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* explains (at section V.D.2), “single-dose studies are considered more sensitive [than multiple-dose studies] in addressing the primary question of BE (i.e., release of the drug substance from the drug product into the system circulation)...”

Despite your assertions about the need for multiple-dose studies, the Petition does not refute the relative advantage of single-dose comparisons.²¹ You state that desmopressin's

¹⁸ See Argenti, D., et al., *A Pharmacokinetic and Pharmacodynamic Comparison of Desmopressin Administered as Whole, Chewed, and Crushed Tablets, and as an Oral Solution*, J. Urology, Vol. 165, 1446 (May 2001) (Aventis study); see also footnotes 23, 30, and 32 *infra*. The Aventis study compared pharmacological responses (pharmacodynamic endpoints), as well as plasma drug concentrations, for various formulations of desmopressin; the study results showed that the pharmacodynamic and pharmacokinetic responses observed were very similar regardless of the formulation tested. *Id.* at 1449 and 1451.

¹⁹ We note that 21 CFR 10.30(b) requires petition signatories to attest that to the best of their knowledge and belief, the petition includes representative data and information known to the petitioner that are unfavorable to the petition.

²⁰ See 21 CFR 320.26(a)(1) (stating generally that, “An in vivo bioavailability or bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults”).

²¹ Although our regulations provide that multiple-dose studies may be necessary in certain circumstances to demonstrate BE (see 21 CFR 320.27), your petition does not contend or substantiate that any of the enumerated circumstances applies or should justify the implementation of a multiple-dose study requirement. We note that 21 CFR 320.27(a)(3)(ii) enables (but does not obligate) us to require multiple-

BA is low; however, current bioanalytical methods are able to measure plasma concentrations of desmopressin accurately and with adequate specificity and reproducibility for purposes of assessing BE. In any event, you present no data to support your assertion that a multiple-dose study requirement would more appropriately address desmopressin's low BA than would a single-dose study. Moreover, if and to the extent that desmopressin's BA may be impacted by food, pH, and other factors, the effect on the BA of a generic oral desmopressin product for which BE to the RLD is established (based on a single-dose study) would not be expected to be significantly different than the effect on the BA of the RLD.

3. ANDA Applicants Do Not Need to Quantify the Duration of Oral Desmopressin's Antidiuretic Action

You state that conventional BE studies are unable to assess the full duration of desmopressin's antidiuretic action due to the unusual potency of the peptide and the inability of current assays to consistently detect the drug at low plasma concentrations that can still exert antidiuretic effects. You claim that the drug's duration of action (which, you contend, if prolonged, could potentially lead to hyponatraemia) can therefore be accurately determined only by pharmacodynamic studies (Petition at 6 to 7; Supplement at ¶¶ 7 and 14).

It is correct that existing analytical techniques may not be able to detect the presence of desmopressin in the body (whether from DDAVP or other any other oral desmopressin product) below certain still-effective levels. However, as addressed above, BE studies are not intended to quantify a drug's duration of action; rather, the purpose of these studies is to determine whether there is a significant difference between the rate and extent of bodily absorption of the active moiety from one drug product and another (e.g., a generic drug product versus its RLD). It is not necessary to measure a drug's total duration of action to evaluate BE based on plasma drug levels. Further, a requirement to measure duration of action could violate the regulatory principle that BA studies should not involve unnecessary testing.²²

dose studies where a drug's BA varies "excessively" from subject to subject. Although you assert that DDAVP's BA varies significantly from subject to subject (Petition at 5), you have not substantiated the relevance of this assertion to BE assessment or 21 CFR 320.27, and we are not aware of any evidence to suggest that the BA for desmopressin varies excessively from subject to subject. While single-dose studies are, as explained above, generally preferable to multiple-dose studies, multiple-dose studies also might be warranted in cases where, for example, a patient population is being studied, and safety considerations and the nature of the patients render single-dose studies infeasible because they would create a disruption in the patients' treatment. In the case of oral desmopressin products (which, as discussed later in this response, are adequately assessed for BE in healthy adults), these considerations do not apply.

²² See 21 CFR 320.25(a)(1). It may be impractical to quantify a drug's duration of action, as there may be an undetermined delay between changes in plasma drug concentration and changes in observed drug effects. Moreover, it may not always be possible to readily or accurately observe or measure a drug's activity (the Petition seems to suggest this in the case of DDAVP (Petition at 11)). Additionally, even where measurable, it may be necessary to administer a drug to patients in more than a single dose in order to assess the drug's effect.

Although potent and of low BA, desmopressin can be detected and accurately measured in plasma over several half-lives, which is adequate to permit an assessment of BE. Indeed, bioanalytical methods for measuring desmopressin in plasma are significantly more accurate and sensitive today than the methods that supported the approval of the RLD, DDAVP.

Moreover, if BE (as ascertained through the measurement of plasma drug concentrations over time) is demonstrated between a generic oral desmopressin product and DDAVP, these drugs would be expected to produce equivalent effects, including duration of clinically significant action. You have presented no evidence to refute this conclusion.²³ We therefore see no substantiated reason to believe that a generic oral desmopressin product that is bioequivalent to DDAVP based on conventional BE testing would be less safe than the RLD in terms of its length of action.²⁴

4. BE Testing in Healthy Adults is Sufficient to Demonstrate BE in Children

As discussed more fully in Section III.B, below, you offer no evidence that BE in children cannot be inferred from BE testing in healthy adults, and we are aware of no such evidence.

5. Reliance on 21 CFR 320.32 and 320.33 is Misplaced

Your petition cites our regulations at 21 CFR 320.32 and 320.33 in support of your request that, based on the attributes of DDAVP discussed above, we require clinical data other than, and in addition to, conventional BE testing to establish the BE of generic oral desmopressin products to their RLD (Petition at 1 and 12 to 13).²⁵ These regulations are not, however, helpful to your request.

²³ Rather, the Petition merely asserts, without providing supportive scientific evidence, that there is “[a] possibility that some [desmopressin] formulations result in prolonged gastrointestinal absorption” (Petition at 6). (The statements of Gary Roberts and José F. Cara, presented as attachment 1 to the Petition and in the Supplement, respectively, include similar assertions without specific substantiation.) In contrast, the Aventis study (also discussed at footnotes 18, 30, and 32) observes that differences in the desmopressin formulations tested (which, through conventional BE testing methods, were determined to be bioequivalent) did not result in differences in the time to onset of drug action or maximum effect, or in the duration of drug action, among these formulations. Aventis study at 1449.

²⁴ Your petition asserts a similar concern that “if [the] bioavailability [of generic oral desmopressin products and the RLD] differ[] in a material way, safety issues [such as water intoxication and the release of the clotting factors von Willebrand Factor and Factor VIII] could arise or effectiveness could diminish” (Petition at 13); however, the Petition does not provide any evidence to support your supposition that conventional BE studies would be inadequate to reveal material differences between the BA of a generic and of the RLD.

²⁵ Page 13 of the Petition includes citations (at footnotes 28 and 29) to 21 CFR 320.24(f)(2) and (f)(6), respectively. Based on the corresponding text in the Petition and a review of 21 CFR 320.24 (which does not include a paragraph (f)), it appears that these citations reflect typographical errors and are intended to reference our regulations at 21 CFR 320.33(f)(2) and (f)(6).

By its terms, 21 CFR 320.32 – which sets forth conditions in accordance with which FDA may seek to establish BE requirements – applies only to “a product not subject to section 505(j) of the [A]ct.”²⁶ This regulation therefore does not apply to ANDAs for generic oral desmopressin products.²⁷

21 CFR 320.33 enumerates criteria to be used in evaluating whether pharmaceutical equivalents and pharmaceutical alternatives are or may not be bioequivalent to one another. 21 CFR 320.32 provides for the evidence and criteria described in 21 CFR 320.33 to be considered in determining whether to issue a proposal for BE testing requirements. Similarly, under 21 CFR 320.22 and 320.23, the criteria in 21 CFR 320.33 have been used to assess whether a drug has a known or potential BE problem and therefore warrants in vivo, rather than in vitro, BE requirements.

The Petition argues that the Agency can require a “unique bioequivalence standard” (Petition at 13) for a drug product satisfying the criteria in 21 CFR 320.33 and that DDAVP is such a drug. However, you offer no evidence to suggest that conventional BE testing would not be adequate to assess BE between a generic oral desmopressin product and DDAVP, and we are aware of no such evidence. Accordingly, as explained above, we see no basis for reassessing the merits of conventional BE testing for these products as you propose.

6. BE Standards for Calcitonin and Metered Dose Inhalers Are Not Relevant to Oral Desmopressin

In support of your request that we determine BE for generic oral desmopressin products based on pharmacodynamic and/or comparative clinical data, you compare desmopressin to calcitonin and drugs administered via metered dose inhalers (MDIs). With respect to calcitonin, you state that this product illustrates how peptides present absorption and equivalence issues. You further state that FDA has chosen to address these issues on a company-by-company basis and should do the same in the case of desmopressin, rather than adopting a uniform approach for demonstrating BE for generic oral desmopressin products (Petition at 13 to 14).

²⁶ 21 CFR 320.32(a).

²⁷ The scope of 21 CFR 320.32’s applicability is explained in the preamble to our 1992 final rule on ANDA requirements. As we stated therein:

Because the 1984 amendments [establishing section 505(j) of the Act] require that any new generic drug products be demonstrated to be bioequivalent to the reference listed drug...additional authority to impose bioequivalence requirements with respect to such products is not needed. However, on its own initiative, the agency has decided not to remove 320.51 [now 21 CFR 320.32] because it establishes a procedure to impose bioequivalence requirements on other classes of drug products not covered by the bioequivalence requirements in the 1984 amendments, including drug products not subject to premarket approval and drug products whose new drug status is not yet determined.

Abbreviated New Drug Application Regulations; Final Rule, 57 FR 17950 at 17978 (April 28, 1992).

The Petition's reliance on calcitonin is not persuasive. Calcitonin does not stand for the proposition that all peptides present absorption and equivalence issues, or that a company-by-company approach to selection of BE methodologies is warranted for any peptide product. Rather, the BE assessment methods deemed appropriate for calcitonin products, which are consistent with applicable BE regulations, simply reflect considerations arising from the dosage forms and routes of administration for those products, which are different than those for oral desmopressin.

Calcitonin is marketed as a solution for subcutaneous or intramuscular injection, and also as a solution for nasal spray. Both of these dosage forms are subject to BE assessment methods that differ from those for solid oral dosage forms such as oral desmopressin. Because of their dosage forms and routes of administration, the general requirement for submission of in vivo data to establish BE can be waived for both injectable and nasal spray calcitonin solutions (see 21 CFR 320.22(b)(1) and (3)).²⁸ Thus, BE for these calcitonin products may be established simply by providing in vitro data. BE assessment methods for calcitonin products therefore do not support the Petition's request that applicants submitting ANDAs for generic oral desmopressin products be required to provide pharmacodynamic or other clinical data, in addition to conventional BE testing, to demonstrate bioequivalence.

The Petition also compares DDAVP to drugs administered via MDIs. As the Petition states, for MDIs, "FDA requires clinical approaches to measuring bioavailability and establishing bioequivalence" (Petition at 14). You observe that, as for the drugs delivered by MDIs, only a small fraction of desmopressin administered in tablet form is available systemically. Therefore, you conclude that FDA should require, in addition to pharmacokinetic data, pharmacodynamic data (as we do for MDIs) to establish BE for generic oral desmopressin products (Petition at 14 to 15).

FDA agrees that DDAVP has low oral bioavailability; however, we disagree with your conclusions regarding the relevance of this property and of the BE standards for MDIs. As noted above, current bioanalytical methods are able to measure and follow plasma concentrations of desmopressin over several half-lives of the drug with acceptable accuracy, specificity, and reproducibility. Unlike the drugs delivered by MDIs, desmopressin is delivered to its site of action by plasma. Therefore, plasma drug concentrations are directly related to the pharmacological action of desmopressin. As earlier explained and reflected at 21 CFR 320.24(b), in vivo plasma drug measurements are the most accurate, sensitive, and reproducible method available – and are superior to the pharmacodynamic or comparative clinical data you have requested – for establishing

²⁸ 21 CFR 320.22(b)(1) and (3) permit BE to be established using in vitro data (if specified conditions are satisfied) for certain drugs whose in vivo BE may be considered self-evident based on other data about the product. These drugs can include parenteral solutions intended for injection and nasal solutions. *Id.* 21 CFR 320.22(b)(1)(ii) provides that the submission of in vivo BE data for a parenteral solution for injection may be waived if the solution "[c]ontains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application." 21 CFR 320.22(b)(3)(ii) and (iii) set forth similar conditions for the waiver of in vivo BE data for nasal solutions.

BE. In contrast with BE for oral desmopressin products, BE for MDIs cannot be established by in vivo plasma drug measurements.

B. Clinical Studies in Children Are Not Warranted to Support ANDAs for Generic Oral Desmopressin Products

You state that desmopressin is indicated primarily for enuretic children, and that the metabolism, pharmacokinetics, and pharmacodynamics of drugs, including desmopressin, can differ substantially between children and adults (Petition at 8 and 15 to 16). You therefore maintain that a generic oral desmopressin product claiming BE to DDAVP in healthy adults may not be bioequivalent in children (Petition at 15 to 16). You conclude that BE between generic oral desmopressin products and DDAVP should be shown through appropriately designed pharmacodynamic or comparative clinical studies in children (Petition at 11 to 12).

FDA does not concur with your contentions. As discussed above, in vivo measurements of plasma drug concentration are the most sensitive, accurate, and reproducible method for establishing BE (including in comparison to the pharmacodynamic studies or clinical trials your petition requests). Moreover, as our regulations specifically provide, BE studies should generally be conducted in normal (healthy) adults.²⁹ Because several factors can influence a drug's BA, BE testing in healthy adults is preferred to control for as many non-drug related variables as possible.³⁰ This approach is the most sensitive, as it best allows any differences in relative BA that are attributable to differences between drug formulations to be revealed.³¹

As earlier discussed, BE studies are not intended to independently establish a drug's safety or effectiveness in a particular subject population; nor is the applicability of the studies' results limited to the subjects used in the studies (e.g., healthy adults). Rather, BE studies submitted in support of ANDAs are designed to help permit a conclusion

²⁹ See 21 CFR 320.25(a)(2) and 320.26(a)(1). 21 CFR 320.25(a)(2) notes that, "In some situations, an in vivo bioavailability study in humans may preferably be done in suitable patients." Your petition does not invoke this provision. Notably, patients are often used for BA testing in cases where a drug product is associated with severe side effects (e.g., clozapine and cytotoxic drugs). See, e.g., the guidance for industry entitled *Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing*, at 1 and 2. Desmopressin is not such a drug. Moreover, the Petition appears to request that testing be performed in healthy children, not in a patient population. In any event, you offer no data to support BE testing for generic oral desmopressin products in either of these populations.

³⁰ We note that the authors of the Aventis study (also discussed at footnotes 18, 23, and 32), which compared the relative BA of different dosage forms of desmopressin, acknowledged that the subjects they used – homogenous, healthy adult males – were chosen to reduce non-drug related sources of variability and thereby enhance comparisons of the test and reference treatments. See Aventis study at 1449.

³¹ Further, testing in other populations would likely lead to greater inter-subject and/or intra-subject variability and therefore necessitate larger study sizes. Additionally, the use of healthy adults is generally preferable to avoid subjecting more vulnerable populations (e.g., healthy children) to the rigors of blood sampling and other discomforts associated with BE testing. See *Report of the Bioequivalence Task Force on Recommendations from the Bioequivalence Hearing Conducted by the Food and Drug Administration, Sept 29 to Oct. 1, 1986* (January 1988) at 4.

(through a comparison of the rate and extent of systemic drug absorption) that a generic drug product proposed for approval can be expected to perform equivalently to the RLD for all of the RLD's approved indications in any approved population. (The approved indications for DDAVP include use in certain children as well as adults.)

As you observe, DDAVP and other oral desmopressin products may behave differently in children than adults. However, you have articulated no scientifically substantiated reason – nor are we aware of any, based on available data concerning desmopressin and other drugs – why a generic oral desmopressin product shown to be bioequivalent to DDAVP in healthy adults would not be bioequivalent to this RLD in the approved pediatric population. Thus, your claim that a generic oral desmopressin product that is bioequivalent to DDAVP in adults may not be bioequivalent in children is unsupported.³²

Although the Petition references, as general support for your requests, the Pediatric Research Equity Act of 2003 (PREA) and related laws, regulations, and guidances that preceded PREA (Petition at 3 (note 5), 15, and 16), we note that ANDAs for generic duplicates of approved drugs are excluded from the scope of PREA's pediatric assessment requirements.³³

C. ANDAs for Generic Oral Desmopressin Products Do Not Need to Include In Vivo BE Data for Each of the RLD's Approved Dosage Strengths

In addition to requesting that we require ANDAs for generic oral desmopressin products to include pharmacodynamic or comparative clinical data to establish BE, your petition requests that separate in vivo BE studies be submitted for each of the RLD's approved dosage strengths. You state that the two approved strengths for DDAVP (0.1 mg and 0.2 mg) do not give proportionally similar drug exposures. You suggest that the differences

³² The statement of Gary L. Robertson submitted as attachment 1 to the Petition asserts that, "It is...possible that age or development have different impacts on absorption of desmopressin from different formulations." However, this conjectural statement, like similar ones in the Petition and Supplement, is not supported by specific data or information; nor does it provide any evidence to support that BE in children cannot be inferred from a showing of BE in healthy adults. Moreover, the authors of the Aventis study (also discussed *supra* at footnotes 18, 23, and 30) expressly noted that if testing in healthy adults establishes BE between different formulations of oral desmopressin, "The expectation is that the test and reference treatments perform equivalently...regardless of age, gender or disease state since drug absorption and disposition have been shown to be independent of the treatment formulation." Aventis study at 1449.

³³ Under PREA (section 505c of the Act), pediatric assessments are required only for applications (or application supplements) submitted under section 505 of the Act or section 351 of the Public Health Service Act that seek approval of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. FDA is also authorized under PREA to require holders of approved applications for already marketed drugs and biological products to conduct pediatric studies under certain circumstances. Products proposed in ANDAs that are generic duplicates of drugs that have been previously approved under section 505 of the Act are not subject to PREA's requirements. Although applications submitted pursuant to an approved suitability petition under section 505(j)(2) of the Act for changes in dosage form or route of administration, or for a new active ingredient in combination, would be subject to the pediatric assessment requirements PREA imposes, such applications are not at issue in your petition.

in exposure may result because the proportions of active and inactive ingredients in tablets for the two approved strengths are not exactly the same. Therefore, you claim that pharmacokinetic and pharmacodynamic data obtained from BA and BE studies using the 0.2 mg tablet cannot be extrapolated to the 0.1 mg tablet, and vice versa, and that separate in vivo studies must be conducted for each strength (Petition at 7 to 8).

FDA does not accept your conclusions. First, your claim of non-proportionality in drug exposure between the 0.1 mg and the 0.2 mg strengths of the RLD has not been substantiated. As documented on page 4 of the publicly available review for NDA 19-955 (DDAVP's NDA) by Tien-Mien Chen, Ph.D., entitled *Review of Two Pharmacokinetic Studies in a New NDA* (Chen review), concerns persisted regarding the specificity of the assay used in the two biostudies (Studies 1 and 2) for DDAVP. Study 2 evaluated the dose proportionality of the two strengths of DDAVP. The accuracy of the pharmacokinetic results of both studies was questionable because of the lack of specificity of the assay used (see Chen review at 4). Furthermore, based on the large variability observed in Study 2, the sample size used was too small to permit definitive conclusions about non-proportionality of drug exposure to be drawn from the results.³⁴ In total, the data in DDAVP's NDA failed to adequately test, let alone demonstrate, a lack of proportionality in drug exposure between the two strengths of DDAVP, and you have not provided (nor are we aware of) other data demonstrating such a lack of proportionality.

Second, you cite our guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE Guidance). You ignore, however, the BA/BE Guidance's discussion of the possibility of waiving in vivo BE testing requirements for lower strengths of a drug product. As the BA/BE Guidance explains:

Waiver of in vivo studies for different strengths of a drug product can be granted under [21 CFR] § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test.

(BA/BE Guidance at 11 to 12) (emphasis in the original).

The BA/BE Guidance makes clear that different strengths of a drug may be proportionally similar in their active and inactive ingredients even if they are not proportionally identical in this regard (see BA/BE Guidance at 12). The amount of active ingredient in a DDAVP tablet is relatively low compared to the total weight of the tablet.

³⁴ See Diletti, E., et al., *Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals*, Int. J. Clin. Pharmacol. Ther. Toxicol., 30 Suppl. 1:S51-8 (1992).

For this reason, desmopressin is considered a high potency drug. As the BA/BE Guidance further explains, high potency drug substances are proportionally similar:

[W]here the amount of the active substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within $\pm 10\%$ of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances^[35] up to and including Level II.

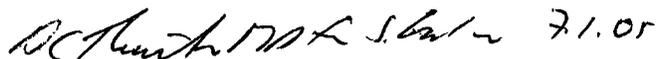
(BA/BE Guidance at 12).

Thus, even if the strengths of a generic oral desmopressin product are not exactly proportional in the ratio of active to inactive ingredients, when the conditions above are satisfied, the Agency will generally waive in vivo BE studies for the lower strength if, based on in vivo studies, BE to the RLD is established for the higher strength.

IV. CONCLUSION

You have failed to present convincing evidence to show that any of the changes you request to demonstrate the BE of generic oral desmopressin products is necessary. Therefore, your petition is denied.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

³⁵ These are the guidances for industry entitled *Immediate Release Solid Oral Dosage Forms – Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*; *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation*, and *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum*.