DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Re: Docket No. FDA-2010-P-0648

Dear Ms. Boskamp and Ms. Manning:

This letter responds to G. Pohl-Boskamp GmbH & Company KG's (Pohl's) citizen petition dated December 16, 2010 (Petition), and Hogan Lovells US LLP's (Hogan Lovells') petition for stay of action dated October 7, 2013 (PSA), submitted on behalf of Pohl. The Petition requests that the Food and Drug Administration (FDA or the Agency) take certain actions with respect to approval of abbreviated new drug applications (ANDAs) for a generic[1] version of Pohl's Nitrolingual Pumpspray (nitroglycerin lingual spray). In the Petition, Pohl requests that FDA refrain from approving an ANDA for nitroglycerin lingual spray based solely on the studies identified and described in the 2010 Draft Bioequivalence (BE) Recommendations for Nitroglycerin Metered Spray/Sublingual products (2010 Nitroglycerin Spray Draft BE Guidance). Pohl also requests that FDA require ANDA applicants to conduct specified stability testing, extractables and leachables testing, and testing for pump functionality. Specifically, Pohl requests that FDA require that ANDA applicants for these products:

1. Include the following for in vivo bioequivalence studies:

    a. Evaluation of the concentrations of the active ingredient (nitroglycerin (TNG)) and its two active metabolites, 1,2- and 1,3-glyceryl dinitrate (1,2-DNG and 1,3-DNG,

[1] The term *generic* refers to a drug product for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act)(21 U.S.C. 355(j)).

respectively) in plasma, and use of a confidence interval approach for the parent substance, TNG

b. Demonstration of bioequivalence using statistical evaluation of an additional pharmacokinetic parameter, partial area under the curve (AUC) at 5 minutes, AUC_{0-5}

2. Adhere to the in vitro study designs recommended in the draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (June 1999) (1999 Nasal Sprays BE Guidance)

3. Conduct stability testing to assure reliability of the finished product after storage in three positions (horizontal, upright, and inverted)

4. Identify, characterize, and/or conduct extractable and leachable testing on all component parts to assure that the plastic and resin materials in the pump device do not diminish the safety or efficacy of the product

5. Test every unit for pump functionality before distribution

The PSA requests that FDA stay the September 20, 2013, approval of ANDA 91-496 submitted by Perrigo Israel Pharmaceuticals Ltd. (Perrigo) until the Agency issues a substantive, written response to the Petition.

As explained below, the Petition has been effectively granted with respect to the requests that in vivo bioequivalence studies include measurement of TNG, 1,2-DNG, and 1,3-DNG in plasma, and that the bioequivalence determination be based on TNG, using a confidence interval approach. The Petition is granted with respect to the requests that extractables and leachables be characterized for all component parts in the pump device, and that every unit be tested for pump functionality before distribution (to the extent described below). The Petition is denied in all other respects. Because this letter is a substantive, written response to the Petition, the PSA is now moot.

I. BACKGROUND

A. Nitrolingual Pumpspray

Nitrolingual Pumpspray, which was originally approved by FDA in October 1985, is a metered dose spray containing the active ingredient nitroglycerin, an organic nitrate.[2] Each bottle of Nitrolingual Pumpspray will deliver 60 or 200 metered sprays containing 400 micrograms of nitroglycerin per spray after priming. The pump must be primed by spraying 5 times into the air before the first use and reprimed every 6 weeks to remain ready for use by spraying the pump 1 time into the air. Nitrolingual Pumpspray contains the following inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, and peppermint oil.

[2] See the product labeling for Nitrolingual Pumpspray (nitroglycerin lingual spray), NDA 18-705; Revised February 2008.

Nitrolingual Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris, *i.e.*, chest pain, due to coronary artery disease.[3] At the onset of an anginal attack, one or two sprays should be administered onto or under the tongue. Nitroglycerin is absorbed from the tongue and surrounding mucosa, producing a therapeutic effect. A spray may be repeated approximately every 3 to 5 minutes as needed. No more than three metered sprays are recommended within a 15-minute period. Nitrolingual Pumpspray may be used 5 to 10 minutes before engaging in activities that might provoke an acute attack.

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter.[4] The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand is decreased by both the arterial and venous effects of nitroglycerin and, presumably, a more favorable supply-demand ratio is achieved. Although the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Nitoglycerin is rapidly metabolized in vivo, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate.[5] Two active major metabolites, 1,2-DNG and 1,3-DNG (the products of hydrolysis), although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolized to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

On September 20, 2013, FDA approved Perrigo's ANDA for nitroglycerin lingual spray (ANDA 91-496).

B. Statutory and Regulatory Standards

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)), which established the ANDA approval process. To obtain approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product. Instead, an ANDA applicant relies on the Agency's previous finding that the reference listed drug (RLD) is safe and effective.[6] To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the proposed generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).[7] In addition, with limited exceptions, an

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[3] Ibid.
[4] Ibid.
[5] Ibid.
[6] A reference listed drug (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 FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."
[7] Under the FD&C Act, "[a] drug shall be considered to be bioequivalent to a listed drug 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

ANDA must contain sufficient information to show that the proposed generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

Drug products that meet the approval requirements under section 505(j) of the FD&C Act generally will be considered by FDA to be "therapeutically equivalent" to the RLD.[8] Drug products are considered to be therapeutic equivalents only if they are "pharmaceutical equivalents" and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[9] Pharmaceutical equivalents contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and meet compendial or other applicable standards of identity, strength, quality, and purity. Pharmaceutical equivalents do not necessarily contain the same inactive ingredients and may also differ in characteristics such as release mechanism, packaging and, within certain narrow limits, labeling.[10] Products classified as therapeutically equivalent can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.[11]

FDA regulations at 21 CFR 314.94(a)(7) set forth the bioequivalence requirements for an ANDA, and 21 CFR 320 sets forth procedures for determining this bioequivalence. The regulations discuss the various methods of determining bioequivalence in descending order of accuracy, sensitivity, and reproducibility. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies (21 CFR 320.24). In addition, § 320.24(b)(6) of the regulations states that an applicant may use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." It is well-accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . . ." (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212, 218 (D.D.C. 1996) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 399-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 863-67 (D.D.C. 1994)).

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either a single dose or multiple doses." See section 505(j)(8)(B)(i); see also implementing regulations at 21 CFR part 320.

[8] Drug products approved in ANDAs submitted under the suitability petition provisions of section 505(j)(2)(C) of the FD&C Act will not be therapeutically equivalent to the RLD that serves as the basis for the petition.

[9] See the Orange Book, 33rd ed., at vii.

[10] See 21 CFR 320.1 and the Orange Book, 33rd ed., at vii, et seq.

[11] Orange Book, 33rd ed., at vii.

C. Bioequivalence Testing

Standard bioequivalence pharmacokinetic studies are conducted using a two-treatment crossover study design, randomly separating a limited number of subjects into test and reference drug groups.[12] Single doses of the test and reference drugs are administered, and blood or plasma levels of the drug are measured over time. The rate and extent of drug absorption are statistically evaluated. The relevant pharmacokinetic parameters calculated from these data include the area under the plasma concentration vs. time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption. The other relevant pharmacokinetic parameter is the maximum or peak drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

For in vivo pharmacokinetic tests, FDA generally considers two products to be bioequivalent when the 90 percent confidence interval for the log transformed ratio of geometric means for the pharmacokinetic parameters, AUC and C_{max}, are entirely within an 80 to 125 percent acceptance interval. The use of an 80 to 125 percent acceptance interval is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the mean of the study data lies in the center of the 90 percent confidence interval, the mean of the data for the test drug is usually close to 100 percent of the mean of the data for the reference drug (a test/reference ratio of 1).[13]

In certain circumstances, FDA recognizes that it is appropriate to use partial AUC as an exposure measure to ensure comparable therapeutic effects.[14] The Agency recommends using partial AUC to assess early exposure in situations calling for more precise control of drug absorption into the systemic circulation:

> For orally administered immediate-release drug products . . . [a]n early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC [AUC_{pR}] as an early exposure measure.[15]

For bioequivalence studies, FDA generally recommends measuring only the parent drug (active drug ingredient or its active moiety in the administered dosage form) rather than its metabolite(s).[16] The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is

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[12] Orange Book, 33rd ed., at viii – ix.

[13] FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence* (January 2001), available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; Orange Book, 33rd ed., at ix.

[14] See FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (March 2003) (BA/BE Guidance), at 9, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[15] See pp. 8-9 of the BA/BE Guidance.

[16] Ibid., pp. 17-18.

more reflective of metabolite formation, distribution, and elimination."[17] In the BA/BE Guidance, FDA describes two situations when the general recommendation (i.e., measuring the parent drug only) does not apply: (1) when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time, or (2) when a metabolite may be formed as a result of gut wall or other presystemic metabolism, and the metabolite contributes meaningfully to safety and/or efficacy.[18]

D. Nitroglycerin Metered Spray/Sublingual Product-Specific Guidance

In February 2010, FDA posted on its Web site the 2010 Nitroglycerin Spray Draft BE Guidance to support ANDAs for nitroglycerin metered spray/sublingual products. In this draft guidance, FDA recommended three studies to demonstrate bioequivalence of generic nitroglycerin metered spray/sublingual products: (1) an in vivo fasting study, (2) an in vitro study of unit dose and uniformity of unit dose, and (3) an in vitro study of priming and tail off.

Pohl submitted the sole comment, dated October 7, 2010, that FDA received on the 2010 Nitroglycerin Spray Draft BE Guidance. In that comment, Pohl raised the following issues that it later reiterated in the Petition:

1. Pohl asked that FDA revise the 2010 Nitroglycerin Spray Draft BE Guidance to require that ANDA applicants evaluate the concentrations of the active ingredient (nitroglycerin (TNG)) and its two active metabolites, 1,2- and 1,3-glyceryl dinitrate (1,2-DNG and 1,3-DNG, respectively) in plasma, and use a confidence interval (CI) approach for the parent substance, TNG.

2. Pohl asked that FDA revise the 2010 Nitroglycerin Spray Draft BE Guidance to require that ANDA applicants demonstrate bioequivalence using statistical evaluation of an additional pharmacokinetic (PK) parameter, partial area under the curve (AUC) at 5 minutes, AUC_{0-5}.

3. Pohl expressed its agreement with FDA's recommendation, set forth in the 2010 Nitroglycerin Spray Draft BE Guidance, that ANDA applicants conduct the following two in vitro studies recommended in the 1999 Nasal Sprays BE Guidance: (1) an in vitro study of the unit dose and the uniformity of the unit dose, and (2) an in vitro study of priming and tail off of the proposed generic product.

Upon further review of the 2010 Nitroglycerin Spray Draft BE Guidance, and upon review of Pohl's comment and the Petition, FDA reconsidered the Agency's draft recommendations and decided to revise them. In November 2011, FDA withdrew the 2010 Nitroglycerin Spray Draft BE Guidance. On February 13, 2012 (77 FR 7586), FDA announced the availability of revised Draft BE Recommendations for Nitroglycerin Metered Spray/Sublingual products (2012 Nitroglycerin Spray Draft BE Guidance).[19] In the 2012 Nitroglycerin Spray Draft BE Guidance,

[17] Ibid., at 18.
[18] Ibid.
[19] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The February 13,

FDA recommends a single study (in vivo fasting study) to demonstrate bioequivalence of generic nitroglycerin metered spray/sublingual products. FDA notes in this revised draft guidance that even though comparative in vitro studies are not requested, the in vitro studies outlined in the 2002 guidance for industry on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*[20] (2002 Nasal Spray CMC Guidance) should be submitted for chemistry, manufacturing, and controls evaluation.

II. DISCUSSION

In the Petition, Pohl requests that FDA require that ANDA applicants for a nitroglycerin lingual spray include the following for in vivo bioequivalence studies: (1) evaluation of the plasma concentrations of the active ingredient, TNG, and its two active metabolites, 1,2-DNG and 1,3-DNG; (2) use of a confidence interval approach for TNG; and (3) demonstration of bioequivalence using statistical evaluation of an additional pharmacokinetic parameter, partial $AUC_{0\text{-}5}$. Pohl also requests that these ANDA applicants: (1) adhere to the in vitro study designs recommended in the 1999 Nasal Sprays BE Guidance, (2) conduct stability testing of the finished product after storage in three positions (horizontal, upright, and inverted), (3) characterize and/or conduct extractables and leachables testing on all component parts of the pump device, and (4) test every unit for pump functionality before distribution. In the PSA, Pohl requests that FDA stay the September 20, 2013, approval of Perrigo's ANDA 91-496 until the Agency issues a substantive, written response to the Petition.

We agree that any ANDA for a nitroglycerin lingual spray that references Nitrolingual Pumpspray as the RLD should evaluate TNG, 1,2-DNG, and 1,3-DNG in plasma, and should base the bioequivalence determination on TNG using a confidence interval approach.[21] Because those recommendations are included in the 2012 Nitroglycerin Spray Draft BE Guidance, the Petition has effectively been granted on those issues. In addition, we agree that such an ANDA should characterize extractables and leachables for all component parts in the pump device, and should provide evidence that every unit has been tested for pump functionality before distribution (to the extent described below).[22] However, we disagree with the other requests in the Petition. Because we are issuing this response to the Petition, the PSA is now moot. We address each of these requests in greater detail below.

2012, *Federal Register* notice noted that Pohl had filed a citizen petition challenging FDA's 2010 Nitroglycerin Spray Draft BE Guidance. The notice stated that FDA was reviewing the issues raised in the Petition and would consider any comments on the Revised Draft Nitroglycerin Spray BE Recommendations before responding to Pohl's citizen petition and finalizing the Agency's bioequivalence recommendation for nitroglycerin metered spray/sublingual products. In the notice, FDA also announced the availability of a revised draft guidance for nitroglycerin metered aerosol/sublingual products.

[20] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[21] Perrigo's ANDA 91-496 for a nitroglycerin lingual spray included such data in the ANDA.

[22] Ibid.

A. Bioequivalence Determinations

1. Parent Drug and Metabolite Measurements

Pohl requests that FDA not approve a nitroglycerin lingual spray ANDA based solely on the studies identified and described in the 2010 Nitroglycerin Spray Draft BE Guidance (Petition at 1 and 9). Specifically, Pohl requests that ANDA applicants for these products evaluate the plasma concentrations of the parent substance, TNG, and its active metabolites, 1,2-DNG and 1,3-DNG; use a confidence interval approach for TNG; and prohibit the substitution of a confidence interval approach only for the active metabolites (Petition at 1, 9-11, and 19). Pohl states that in accordance with the 2010 Nitroglycerin Spray Draft BE Guidance, FDA would permit ANDA applicants for these products to employ a confidence interval approach only for the two active metabolites, 1,2-DNG and 1,3-DNG, if TNG cannot be reliably measured (Petition at 1 and 10). Pohl asserts that FDA should not allow ANDA applicants this flexibility because numerous studies, which Pohl cites, have demonstrated that TNG can be reliably and accurately measured using analytical methods employing gas chromatography (Petition at 1, 2, and 10).

Pohl asserts that if bioequivalence is based on equivalence of the dinitrate metabolites of TNG, there would not be assurance that a generic nitroglycerin lingual spray could offer "the clinically necessary early relief described in the labeling of the RLD" (Petition at 10 and 11). Pohl bases its assertion on a study[23] that Pohl claims demonstrates that the half-lives (35 and 38 minutes) and time to maximum concentration (T_{max}) (13 and 17 minutes) of the dinitrate metabolites are significantly longer than for TNG,[24] and occur long after symptom relief is typically experienced (Petition at 10). Pohl also claims that based on another study,[25] the metabolites have very low potency, which reflects their relative insignificance to the drug product's clinical effects (Petition at 11).[26]

Pohl raised this same issue in its comment on the 2010 Nitroglycerin Spray Draft BE Guidance. In 2012, upon further review of the 2010 Nitroglycerin Spray Draft BE Guidance, and upon review of Pohl's comment and the Petition, FDA agreed that TNG can now be reliably measured using current analytical techniques such as gas chromatography and that, in accordance with the BA/BE Guidance, TNG should be used for demonstration of bioequivalence. FDA therefore revised the 2010 Nitroglycerin Spray Draft BE Guidance to remove the option for the bioequivalence determination to be based on the two active metabolites, 1,2-DNG and 1,3-DNG (see the 2012 Nitroglycerin Spray Draft BE Guidance[27]). Nonetheless, because the two

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[23] Jensen KM and Dahl JB. Plasma concentrations of glyceryl trinitrate and its dinitrate metabolites after sublingual administration to volunteers: Simultaneous determination of glyceryl trinitrate and its nitrate metabolites. *Arzneim.-Forsch./Drug Res.* 44: 951-953, 1994.

[24] Ibid. Jensen and Dahl reported a half-life of 3.3 minutes and a T_{max} of 4.9 minutes for TNG. Elsewhere in your petition, you cite a publication by Santoro, A. et al. for the point that the half-life of TNG is 1 to 3 minutes (Petition at 11). You also reference Nitrolingual Pumpspray's approved labeling for the T_{max} of TNG (7.5 minutes) (Petition at 11).

[25] Needleman P, Blehm DJ, and Rotskoff KS. Relationship between glutathione-dependent denitration and the vasodilator effectiveness of organic nitrates. *J. Pharmacol. Exp. Ther.* 165: 286-287, 1969.

[26] However, elsewhere in the Petition, Pohl states that the dinitrate metabolites are believed to contribute to the therapeutic effect of TNG (Petition at 10).

[27] We note that this discussion regarding the 2010 Nitroglycerin Spray Draft BE Guidance and the 2012 Nitroglycerin Spray Draft BE Guidance is limited to the issues raised in the Petition, and does not constitute a full

metabolites, 1,2-DNG and 1,3-DNG, may contribute to the pharmacological activity of Nitrolingual Pumpspray, we recommend that pharmacokinetic data from them be submitted as supporting evidence. For bioequivalence determinations, the 2012 Nitroglycerin Spray Draft BE Guidance recommends using a 90% confidence interval approach for TNG, consistent with Pohl's request. However, if there is evidence of high variability in the AUC and/or C_{max} parameters (i.e., within-subject variability $\geq$ 30%), a reference-scaled average bioequivalence approach for TNG may be used (see the 2012 Nitroglycerin Spray Draft BE Guidance). These bioequivalence recommendations are the same as those recommended for nitroglycerin sublingual tablet/oral products.[28]

For these reasons, Pohl's request on this issue has been effectively granted.

2. Partial AUC Determination

Pohl requests that FDA require ANDA applicants for a generic nitroglycerin lingual spray to demonstrate bioequivalence using statistical evaluation[29] of a pharmacokinetic parameter, AUC_{0-5}, in addition to the Agency's traditional pharmacokinetic parameters, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Petition at 2, 9, 11, 12, and 19). Pohl claims that FDA's standard pharmacokinetic measures alone are inadequate for a generic nitroglycerin lingual spray because of the product's rapid onset of clinical effect, which Pohl reports usually occurs within 2 to 3 minutes after administration[30] (Petition at 2 and 11). Pohl asserts that to assure the necessary relief of symptoms and the therapeutic equivalence of a generic to Nitrolingual Pumpspray, ANDA applicants must evaluate their product at the "clinically relevant early exposure period" (Petition at 2, 11, and 12). Pohl alleges that a delay in therapeutic effectiveness will likely cause patients anxiety, confusion, and even panic, particularly in those situations where symptoms of angina pectoris have arisen from emotional stress and that, if not properly treated, angina pectoris may cause permanent myocardial damage (Petition at 12). Pohl also claims that inadequate treatment increases the risk of misdiagnosis as unstable angina, because symptoms appear unresponsive to TNG.

Pohl states that Nitrolingual Pumpspray's C_{max}, T_{max} and mean AUC are 1,041 picogram (pg)/milliliter (mL), 7.5 minutes, and 12,769 pg(min)/mL, respectively, [31] and claims that this indicates that the peak of its pharmacokinetic profile occurs significantly later than the "clinically relevant time interval of 3 to 5 minutes, when relief from symptoms of angina pectoris must occur" (Petition at 11 and 12). Pohl alleges that a generic nitroglycerin lingual spray could match Nitrolingual Pumpspray's C_{max}, T_{max}, and general AUC without demonstrating an equivalent early absorption, as would be measured by AUC_{0-5}, and without delivering the same

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review or finalization of the draft BE guidance for nitroglycerin spray ANDAs. The draft guidance, when finalized, will represent FDA's current thinking on these topics.

[28] See Draft BE Recommendations for Nitroglycerin Sublingual Tablet/Oral products (Feb. 2011), available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[29] Pohl requests that the AUC_{0-5} parameter be evaluated using a 90% confidence interval, including, if necessary, a reference-scaled approach to mitigate the impact of any higher intra-subject variability (Petition at 12).

[30] See Santoro A, Rovati, L, Follet M, Setnikar I, Caplain H, and Gualano V. Plasma levels of glyceryl trinitrate and dinitrates during application of three strengths of a new glyceryl trinitrate transdermal patch. *Arzneim.-Forsch./Drug Res.* 50: 787, 2000.

[31] Product labeling for Nitrolingual Pumpspray (nitroglycerin lingual spray), NDA 18-705; Revised February 2008.

clinically relevant dose as that described in the approved labeling (Petition at 12). Pohl asserts that if only the traditional pharmacokinetic parameters of C_{max} and AUC are evaluated, FDA would not be able to determine whether a generic nitroglycerin lingual spray product would be effective within the initial 3 to 5 minute time period and, thus, whether it would be entitled to the same labeling as Nitrolingual Pumpspray (Petition at 12).

Pohl states that FDA's BA/BE guidance recommends use of a partial AUC truncated at T_{max} for products demonstrating clinically important early exposure, such as orally administered immediate-release drugs with rapid onset of effect (Petition at 7). However, Pohl alleges that FDA subsequently retreated from this position in several petition responses[32] (Petition at 7). Pohl further states that FDA does not categorically require additional pharmacokinetic parameters and has refused to apply its statistical criteria to T_{max} and partial AUC measures[33] (Petition at 7-8). On the other hand, Pohl states that in August 2009, FDA issued draft individual bioequivalence recommendations for Ambien CR (zolpidem tartrate extended release) that included the use of partial AUC measurements. Pohl also states that on April 13, 2010, the Office of Generic Drugs acknowledged at a meeting of FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology the importance of the use of partial AUC measures for drugs with complex pharmacokinetic profiles such as "multiphasic modified release products" that contain both immediate release and extended release components, including Ambien CR and modified release methylphenidate (Petition at 8). For Ambien CR, Pohl notes that FDA recommended that $AUC_{0\text{-}1.5\ hours}$ and $AUC_{1.5\ hours-t}$ replace $AUC_{0\text{-}t}$ because these partial AUC measurements correspond to periods of sleep onset and sleep maintenance which Pohl asserts that FDA identified as clinically relevant time intervals[34] (Petition at 8).

Pohl raised this same issue in its comment on the 2010 Nitroglycerin Spray Draft BE Guidance. In 2012, upon further review of the 2010 Nitroglycerin Spray Draft BE Guidance, and upon review of Pohl's comment and the Petition, FDA declined to include a recommendation that the pharmacokinetic parameter, $AUC_{0\text{-}5}$, be used in addition to traditional PK parameters, C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, to demonstrate bioequivalence for a generic nitroglycerin lingual pumpspray product. We disagree with the request in the Petition that FDA require evaluation of the additional pharmacokinetic parameter, $AUC_{0\text{-}5}$, for two reasons: (1) the lack of data to establish that the partial AUC measurement at 5 minutes predicts the rapid onset of clinical effect for a nitroglycerin lingual pumpspray product, and (2) the lack of complexity in the Nitrolingual Pumpspray formulation and drug exposure profile.

First, the Petition does not include data to establish a meaningful relationship between the pharmacokinetic parameter $AUC_{0\text{-}5}$ and the timing of the onset of clinical effect for a nitroglycerin lingual pumpspray product. It is not possible to conclude that a specific level of

[32] As an example, Pohl cites FDA's citizen petition response on Carbatrol, Docket No. FDA-2008-P-0532 (Mar. 31, 2009), p. 3, fn. 8.

[33] As an example, Pohl cites FDA's citizen petition response on felodipine, Docket No. FDA-2007-P-0123 (Apr. 17, 2008), p. 10.

[34] To support Pohl's claim, Pohl cites FDA's draft BE recommendations for zolpidem tartrate. These recommendations have been finalized and are available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf. Pohl also cites FDA's citizen petition response on Ambien CR (zolpidem tartrate), Docket No. FDA-2007-P-0182 (Oct. 13, 2010).

TNG at 5 minutes is necessary to achieve equivalent effect because the clinical effect of Nitrolingual Pumpspray likely results from a combination of the effects of TNG and its metabolites, but the individual contribution of each analyte to the clinical effect is not known.

Indeed, data from an NDA supplement[35] highlight the absence of a clear relationship between AUC_{0-5} and clinical effect. Nitrolingual was initially approved on October 31, 1985 as an aerosol. In 1997, FDA approved a supplement that sought approval for a reformulated version of Nitrolingual that delivered nitroglycerin without propellants by using a metered pumpspray mechanism. In support of the supplement, Pohl submitted the results from a bioequivalence study comparing the aerosol and pumpspray products.[36] The study showed that the two products had significantly different pharmacokinetic profiles and were, thus, "bioinequivalent." Pohl then conducted a double-blind, placebo-controlled clinical trial to demonstrate the efficacy and safety of the pumpspray product.[37] The clinical trial yielded the expected results, so FDA approved the pumpspray product through a supplement to the previously-approved NDA, with only slight revisions to the labeling that had been approved for the aerosol product. This data thus suggests that a generic nitroglycerin lingual spray could have the same clinical effect as Nitrolingual Pumpspray, notwithstanding differences in AUC_{0-5}.

Moreover, the labeling for Nitrolingual Pumpspray indicates that there is a broad range of exposure (C_{max} and AUC) and efficacy endpoint relationships for that product, and that the pharmacokinetic profile for the first five minutes therefore is not a clinically significant parameter.[38] For example, the labeling contemplates that a patient may not experience relief within 3 to 5 minutes, and provides that such a patient may repeat the dose every 3 to 5 minutes, so as long as dosing does not exceed three sprays within a 15-minute period. In addition, the labeling appears to contemplate that clinical effect may be achieved beyond 5 minutes post-dosing: it states that "Nitrolingual Pumpspray may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack."

Second, Nitroglycerin Pumpspray lacks the type of complex formulation or pharmacokinetic profile that may warrant the use of a partial AUC parameter. Other products for which we have recommended use of partial AUC for demonstration of bioequivalence, such as Ambien CR and methylphenidate hydrochloride extended release, have complex formulations that are designed to have multiple distinct release phases. For example, Ambien CR consists of a coated two-layer tablet, one layer that releases drug content immediately and the other layer that allows a slower release of additional drug content.[39] The pharmacokinetic profiles of these products demonstrate complex exposure profiles with multiple peaks or prolonged plateaus.[40] On the other hand,

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[35] Nitrolingual Pumpspray (nitroglycerin lingual spray) (NDA 18-705, Supplement SCF 006).
[36] Ibid.
[37] Ibid.
[38] Product labeling for Nitrolingual Pumpspray (nitroglycerin lingual spray), NDA 18-705; Revised February 2008. Product labeling for NitroMist (nitroglycerin) lingual aerosol, NDA 21-780; Revised March 2011. Product labeling for Nitrostat (nitroglycerin sublingual tablets, USP), NDA 21-134; Revised May 2011.
[39] Product labeling for Ambien CR (zolpidem tartrate extended-release) tablets, NDA 21-774; Revised 2013.
[40] See FDA's July 19, 2012, response to Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and UCB, Inc.s' citizen petitions regarding methylphenidate extended-release products available on the Internet at http://www.regulations.gov/#!documentDetail;D=FDA-2004-P-0151-0011 and FDA's draft BE recommendations for methylphenidate extended release capsule products, available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320005.pdf and

nitroglycerin lingual spray, an immediate release product with relatively rapid absorption, has a simple pharmacokinetic profile that is well characterized by the pharmacokinetic parameters, AUC, C_{max}, and T_{max}, without the need for an additional metric. For these reasons, we deny Pohl's request.

3. Comparative In Vitro Tests

Pohl requests that FDA require that ANDA applicants for a generic nitroglycerin lingual spray adhere to the in vitro study designs recommended in the 1999 Nasal Sprays BE Guidance[41] (Petition at 2). Pohl states that the 2010 Nitroglycerin Spray Draft BE Guidance requires that these ANDA applicants conduct two in vitro studies: (1) an in vitro study of unit dose and uniformity of unit dose and (2) an in vitro study of priming and tail off. Pohl further states that the 2010 Nitroglycerin Spray Draft BE Guidance elaborates on required designs for these studies and suggests that the Nasal Sprays BE Guidance provides adequate parameters for study design, conduct, and analysis.

Pohl raised this same issue in its comment on the 2010 Nitroglycerin Spray Draft BE Guidance. There, Pohl expressed support for the recommendation set forth in the draft guidance for the two in vitro studies. In 2012, upon further review of the 2010 Nitroglycerin Spray Draft BE Guidance, and upon review of Pohl's comment and the Petition, FDA determined that conduct of an in vivo fasting study is sufficient to demonstrate bioequivalence of generic nitroglycerin metered spray/sublingual products, and that comparative in vitro tests are not necessary. Therefore, in the 2012 Nitroglycerin Spray Draft BE Guidance, FDA removed the recommendation for the two in vitro studies (see the 2012 Nitroglycerin Spray Draft BE Guidance for these products, described in section I.D of this document). We disagree with Pohl's request in the Petition that FDA require those two in vitro studies. FDA has concluded that because TNG is a systemically acting drug product, an in vivo fasting study is sufficient to identify differences in drug absorption between a generic nitroglycerin lingual spray and its RLD resulting from differences in formulation and/or device performance. Additional comparative in vitro tests are not necessary to demonstrate bioequivalence for these products.

However, we continue to recommend conduct of in vitro studies for chemistry, manufacturing, and controls (CMC) evaluation. To ensure constant device performance of a generic nitroglycerin lingual spray throughout its life, in vitro studies as outlined in the 2002 Nasal Spray CMC Guidance[42] should be conducted, including tests for unit dose and uniformity of unit dose

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf. See also FDA's October 13, 2010, response to sanofi-aventis U.S. LLC's citizen petition regarding Ambien CR, available on the Internet at http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0182-0017 and FDA's BE recommendations for zolpidem extended release tablets, available on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf.

[41] Note that the 1999 Nasal Sprays BE Guidance, which FDA issued previously in draft, has been superseded by a new draft guidance for industry on this topic, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003) (2003 Nasal Sprays BE Draft Guidance), available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[42] We note that even though the 2002 Nasal Spray CMC Guidance does not specifically apply to lingual sprays, this guidance can be used as a reference for recommendations on appropriate in vitro study design, conduct, and data analysis of lingual sprays.

and priming and tail off. A proposed generic nitroglycerin lingual spray product would need to meet prespecified criteria set for these studies to be acceptable for approval.

B. Chemistry, Manufacturing, and Controls (CMC) Information

1. Stability Testing

Pohl states that the critical stability requirements for a generic nitroglycerin lingual spray include pump delivery, spray content uniformity, and priming and repriming standards, and requests that FDA require all ANDA applicants for these products to conduct stability testing after storage in three positions: horizontal, upright, and inverted (Petition at 2, 13, 15, and 19). Pohl claims that this testing is necessary to assure that a generic nitroglycerin lingual spray can reliably provide critical relief to patients suffering from angina pectoris, even after a canister of drug product has gone unused for long periods of time while being carried or held in various positions (Petition at 2).

Pohl requests that this testing be conducted in accordance with a stability protocol that Pohl states was developed by Dr. Stuart Zimmerman at FDA, and that Pohl claims that it was required to perform for approval of NDA supplements (Petition at 13). Pohl claims that this protocol outlines a comprehensive stability testing program to assure that the pumpspray delivers the labeled dose over the course of the product's shelf life (Petition at 5). Specifically, Pohl requests that the stability testing be conducted after storage in the three positions (horizontal, upright, and inverted), with sampling at monthly to 6-monthly intervals for a total of 21 months with product stored at 30° Celsius and at weekly to 6-weekly intervals for a total of 21 weeks with product stored at 40° Celsius (Petition at 13).

Pohl claims that although Dr. Zimmerman's protocol required stability testing to be done in three orientations (horizontal, upright, and inverted), FDA's 2002 Nasal Spray CMC Guidance[43] recommends that primary stability studies should be conducted after storage under different orientations (upright and inverted or upright and horizontal), to characterize any differences in behavior under storage (Petition at 15). Pohl states that, in this guidance, FDA recommends that if these stability studies demonstrate that storage orientation has no effect on product quality, routine stability studies can be conducted on product stored in only one orientation (Petition at 15). Pohl claims that because of the labeled instructions for dosing and priming/repriming of Nitrolingual Pumpspray, FDA must require that ANDA applicants for generic nitroglycerin lingual sprays follow the requirements contained in Dr. Zimmerman's protocol (Petition at 15).

We agree that pump delivery, spray content uniformity, and priming and repriming standards constitute critical stability requirements for a generic nitroglycerin lingual spray and, therefore, recommend that ANDAs for these products include data for these tests. We also agree that these ANDAs should include stability testing conducted under a variety of storage conditions, including different orientations and storage temperatures, as part of the characterization studies for these products. However, we disagree with Pohl's request that these ANDA applicants conduct stability testing in three orientations at specific sampling intervals in accordance with

[43] Pohl notes that FDA typically looks to its 2002 Nasal Spray CMC Guidance for CMC standards for lingual sprays (Petition at 9).

the stability protocol developed by Dr. Zimmerman.[44] As Pohl notes, we have issued more recent guidance on this topic. Accordingly, we recommend that ANDA applicants follow the CMC recommendations in the 2002 Nasal Spray CMC Guidance that would be applicable to lingual sprays.[45] In accordance with this guidance, primary stability studies should include storage under different orientations (e.g., upright and inverted or upright and horizontal) to characterize any differences in the behavior under storage. Then, once sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation. Recommendations on appropriate test storage conditions (e.g., temperature conditions) are described in the ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products* (Q1A(R2) ICH Guidance).[46] In addition, stability test intervals should be indicated in the protocol. Nonetheless, upon review of an ANDA for a lingual spray, we may ask for additional CMC information to provide assurance of product effectiveness and quality, including requests for stability testing in additional orientations and at additional sampling times.

2. Extractable and Leachable Testing

Pohl requests that FDA require that ANDA applicants for a generic nitroglycerin lingual spray conduct detailed extractable and leachable testing for all device components (Petition at 2 and 15). Pohl claims that this testing is necessary because nitroglycerin is well-known to interact with component materials, and this testing will assure that the nitroglycerin does not react with the plastic and resin materials in the pump device in such a way as to diminish the safety and efficacy of the product (Petition at 2, 15, and 16). Pohl specifically requests that each plastic or resin within each device component touching the active ingredient be shown by the ANDA applicant or by its component manufacturer(s) to be safe and nonreactive when used with TNG (Petition at 16). Pohl claims that unknown effects caused by leaching or extraction could result in a delivered dose that contains an ineffective amount of active ingredient or unsafe levels of container residue (Petition at 16). Pohl cites the 2002 Nasal Spray CMC Guidance to support its request:

> Relevant information ... should be provided on the characteristics of each of the critical components of the container closure system to ensure its suitability for manufacturing the drug product. Information should also be provided on acceptance criteria, test procedures, and analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) for the critical components. Critical components are defined as (1) those that contact the patient (mouth or nose) or the formulation, (2) those that affect the mechanics of the overall performance of the device, or (3) any protective packaging.[47]

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[44] Pohl correctly notes that ANDA applicants are not required to conduct identical CMC or stability testing as that performed for the RLD. Petition at 13.

[45] We note that even though the 2002 Nasal Spray CMC Guidance does not specifically apply to lingual sprays, some of the stability studies outlined in the guidance are applicable for demonstrating quality and performance characteristics of lingual sprays.

[46] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[47] 2002 Nasal Spray CMC Guidance at 23 – 24.

Pohl also states that the 2002 Nasal Spray CMC Guidance outlines a comprehensive list of quality attributes with regard to the pumpspray design components, including the following, which must be included in the ANDA:[48]

- Composition and quality of materials of the container, closure, and pump components
- Control extraction methods and data for elastomeric and plastic components
- Toxicological evaluation of extractables
- Qualitative and quantitative extractable profiles from the container, closure, and pump components[49]

We agree with Pohl's request. We recommend that ANDA applicants[50] for lingual sprays include characterization of leachables during stability testing of these products as described in the 2002 Nasal Spray CMC Guidance. This guidance contains recommendations on evaluation of compounds that leach from elastomeric or plastic components of the container closure system and provides validated analytical procedures to identify, monitor, and quantify leached components.

We also recommend that ANDA applicants for lingual sprays include information from controlled extraction studies as described in the 2002 Nasal Spray CMC Guidance. This guidance contains recommendations on obtaining quantitative extractable profiles for elastomeric or plastic packaging components under specified test conditions and on establishing an acceptance criterion for each of the extractables from the container, closure, and critical components of the pump used in submitted batches. The guidance specifies that a qualitative approach for control of the extractable profile may suffice for critical components that affect the mechanics of the overall performance of the device but do not come into contact with either the patient or the formulation. For these reasons, we grant Pohl's request.

3. Pump Functionality Testing

Pohl requests that FDA require that ANDA applicants for a generic nitroglycerin lingual spray test every unit for pump functionality before distribution, as Pohl states that it does (Petition at 3 and 17). Pohl states that it primes each bottle using an automatic device so that the pump system will be filled with active solution. Once the bottle is primed, Pohl indicates that the automatic device depresses the pump and the subsequent spray shot(s) are recorded using a camera system (Petition at 17-18). Pohl states that the functioning of each unit is then evaluated, and only bottles that pass this testing are released for distribution and sale. Pohl indicates that bottles that do not demonstrate functionality are rejected.

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[48] In accordance with the 2002 Nasal Spray CMC Guidance (p. 24), Pohl notes that reference to information in Drug Master Files (DMFs) for container, closure, and pump information is acceptable if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and unique identifier) to the pertinent and up-to-date information (21 CFR 314.420(d)).

[49] 2002 Nasal Spray CMC Guidance at 24.

[50] In accordance with the 2002 Nasal Spray CMC Guidance, reference to information in a DMF for container, closure, and pump information is acceptable if the DMF holder provides written authorization that includes specific reference to the pertinent and up-to-date information.

Pohl claims that this testing is critical for patients who require each nitroglycerin lingual spray to perform quickly and reliably despite infrequent use over the labeled shelf life of the product (Petition at 3 and 17). Pohl alleges that a malfunctioning pumpspray mechanism will not effectively deliver drug to a patient with angina pectoris and may also cause the patient to panic and become distressed (Petition at 3).

We agree, in general, with Pohl's request because we expect that applicants for these types of products will test each unit for pump functionality before distribution. However, alternative approaches may be acceptable. FDA considers both the probability of product failure and the severity of product failure in a risk-based analysis in evaluating the CMC quality control strategy proposed in an ANDA. For a rescue medication such as nitroglycerin lingual spray where there would be a severe adverse effect from product failure, FDA would generally expect that testing of all device units would be part of the applicant's control strategy. However, if an applicant provides adequate data to support a control strategy that does not involve testing every unit, such an approach could be acceptable.

Therefore, we grant Pohl's request to the extent described above.

C. Request for Stay

In the PSA, Pohl requests that FDA stay the September 20, 2013, approval of Perrigo's ANDA 91-496 until the Agency issues a substantive, written response to the Petition. Pohl sought this stay because the Petition remained unanswered despite approval of Perrigo's ANDA. Pohl claims that this is contrary to fundamental tenets of the Administrative Procedure Act and the Agency's customary practice. Pohl requests that FDA provide a response to the PSA by October 31, 2013.[51]

Because this letter contains our response to the Petition, the PSA is moot.[52]

III. CONCLUSION

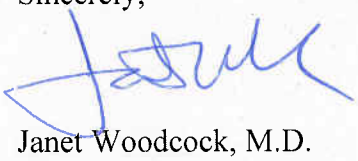
For the reasons discussed above, the Petition has been effectively granted with respect to Pohl's request that an ANDA for a nitroglycerin lingual spray that references Nitrolingual Pumpspray as the RLD evaluate TNG, 1,2-DNG, and 1,3-DNG in plasma, and base the bioequivalence determination on TNG using a confidence interval approach. The petition is granted with respect to Pohl's request that such an ANDA be required to characterize extractables and leachables for all component parts in the pump device, and provide evidence that every unit has been tested for

[51] In a submission dated October 18, 2013, Olsson Frank Weeda Terman Matz PC commented on the PSA on behalf of Perrigo.

[52] Although FDA generally tries to respond to citizen petitions at the same time that it approves applications that are the subject of those petitions when doing so would not delay the approval, there is no requirement that FDA delay an approval action because a petition was filed, but the Agency has not yet issued a response. *See Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 162 (D.D.C. 2006); 21 CFR 10.35(d).

pump functionality before distribution (to the extent described). The Petition is denied in all other respects, and the PSA is now moot.

Sincerely,



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