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## Appendix C. Background on OGD's Approval of Generic Copies of EMLA<sup>®</sup> Cream Based on Pharmacokinetics

On July 1, 2002, Altana, Inc., submitted an ANDA for a generic version of EMLA Cream with a pharmacokinetic study rather than a clinical endpoint study to demonstrate bioequivalence.<sup>199</sup> The primary reviewer for the ANDA, Surendra P. Shrivastava, Ph.D., correctly determined that a pharmacokinetic study was "not appropriate" because the drug was "not intended to be absorbed into the blood stream, and the bioavailability assessed by measuring plasma levels during [a] 36 hour period does not measure or reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [21 CFR 320.23a(1)] during 0-4 hour treatment period."<sup>200</sup> Dr. Shrivastava further noted:

The systemic absorption of the drug product is a side effect (toxic) of the desired local effect. The amount of drug available on the surface of the skin depends on the diffusion constant, partition coefficient of drug between skin and vehicle, and concentration gradient. The systemic drug level, on the other hand, depends on [a] number of factors, e.g., drug absorption, distribution, metabolism, elimination, patients' weight, etc. Therefore, [a] pharmacokinetic approach is not appropriate for measuring bioavailability (efficacy) of topicals.<sup>201</sup>

In addition, Dr. Shrivastava noted that blood levels at 24 hours represented less than 1% of the total applied dose, and considerably less at the therapeutically relevant timeframe of 3 hours. "This is too small [of a] sample compared to what is bioavailable on the treated skin surface to provide any confidence in the data."<sup>202</sup>

Based on his analysis of the drug product and FDA regulations, Dr. Shrivastava recommended that the sponsor's proposed pharmacokinetic study was unacceptable. "The firm is requested to conduct [a] clinical study to establish bioequivalence of this product."<sup>203</sup>

Dr. Shrivastava's comments were consistent with OGD's longstanding interpretation of FDA's bioequivalence regulations as applied to topical dermatologic products, as discussed above.<sup>204</sup> Moreover, existing Guidance documents for orally administered drug products, corticosteroids, and nasal aerosols and sprays indicated that locally acting products required pharmacodynamic or clinical endpoint studies to demonstrate bioequivalence.

Despite the sound scientific basis of Dr. Shrivastava's analysis, the plain language of existing regulations and Guidance documents, and repeated public statements by Agency officials, OGD's Team Leader for the ANDA review, Shriniwas G. Nerurkar, Ph.D., dismissed Dr. Shrivastava's review as "opinion."<sup>205</sup> Dr. Nerurkar instead stated that "management" in OGD's

<sup>199</sup> See GENERIC EMLA APPROVAL PACKAGE, *supra* note 91.

<sup>200</sup> Shrivastava, *Division of Bioequivalence Review*, *supra* note 91 (bracketed citation in original).

<sup>201</sup> *Id.*

<sup>202</sup> *Id.*

<sup>203</sup> *Id.*

<sup>204</sup> See *supra* notes 70 to 80 and accompanying text.

<sup>205</sup> Nerurkar, *Division of Bioequivalence Review*, *supra* note 92.

Division of Bioequivalence “in consultation with the medical officers of the FDA has determined that a bioequivalence study with clinical end points is not necessary for this locally acting drug product and a bioequivalence study with PK [pharmacokinetic] end points is acceptable.”<sup>206</sup>

Dr. Nerurkar did not offer any scientific justification for this decision. Rather, he identified “precedent” that he felt necessitated comparable treatment regarding acceptable bioequivalence studies. In particular, Dr. Nerurkar noted that two prior ANDAs for the same product had been found to have acceptably demonstrated bioequivalence using pharmacokinetic rather than clinical endpoint studies.<sup>207</sup> Although these two drugs had not yet been approved, Dr. Nerurkar explained that a medical consult with the Team Leader of the Anesthetic Drug Group within FDA’s Division of Anesthetic, Critical Care, and Addiction Drug Products had suggested that as long as a full set of pharmacokinetic data could be obtained, it “would seem appropriate” to use a standard pharmacokinetic bioequivalence study rather than a study with clinical endpoints.<sup>208</sup> “Because of this precedent and the fairness issue,” wrote Dr. Nerurkar, “the DBE [Division of Bioequivalence] can not deem Altana’s ANDA unacceptable.”<sup>209</sup>

Significantly, it appears that the first inquiry from a generic sponsor regarding methods of demonstrating bioequivalence to EMLA proposed a bioequivalence study with clinical endpoints rather than pharmacokinetics. Consequently, a medical reviewer recommended that the Division of Anesthetic, Critical Care and Addiction Drug Products be consulted regarding the proposed clinical trial protocol, not whether pharmacokinetics were adequate to demonstrate bioequivalence.<sup>210</sup> However, while the publicly available record is incomplete, it appears that a

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<sup>206</sup> *Id.*

<sup>207</sup> *Id.* (referring to drug products subsequently approved as ANDA Nos. 76-290 and 76-320).

<sup>208</sup> Memorandum from Bob A. Rappaport, M.D., Deputy Director, Division of Anesthetic, Critical Care, and Addiction Drug Products, FDA, and Team Leader, Anesthetic Drug Group, FDA, to Harvey A. Greenberg, R.Ph., OGD, FDA (Oct. 5, 2000) [hereinafter Rappaport Memorandum], in *GENERIC EMLA APPROVAL PACKAGE*, *supra* note 91 (stating, in response to OGD request for consultation regarding demonstrating bioequivalence for a generic version of EMLA Cream, that because “a full set of pharmacokinetic data could be obtained . . . [i]t would seem appropriate that a standard bioequivalence study could be the accepted criterion for approval of a generic product using EMLA as the reference listed drug.”). *See also* Letter from Gary J. Buehler, Director, OGD, FDA, to Dr. Masson (Nov. 13, 2000), *in id.* (informing a private party that a standard pharmacokinetic study along with a skin sensitization test would be sufficient to demonstrate bioequivalence to EMLA Cream); Mary M. Fanning, Associate Director for Medical Affairs, OGD, FDA, *Medical Officer Review* (Oct. 10, 2000), *in id.* (recommending that a standard pharmacokinetic study should be sufficient to approve a generic EMLA cream, based on consultation with the Division of Anesthetic, Critical Care, and Addiction Drug Products); Mary M. Fanning, Associate Director for Medical Affairs, OGD, FDA, *Medical Officer Review* (Sept. 22, 2000), *in id.* (recommending that the Division of Anesthetic, Critical Care, and Addiction Drug Products be consulted as to whether a generic sponsor’s proposed bioequivalence study with clinical endpoints was sufficient to demonstrate bioequivalence to EMLA and that the Division of Dermatological and Dental Drug Products be consulted as to whether skin sensitization studies could be conducted in conjunction with clinical endpoint studies). It is unclear why FDA’s Division of Dermatological and Dental Drug Products was not consulted on the proposed clinical endpoint and pharmacokinetic studies, but instead only consulted regarding the proposed skin sensitization study, particularly in light of the fact that its Director, Dr. Jonathan Wilkin, M.D., had been so heavily involved in review of alternatives to clinical endpoint bioequivalence studies for topical products.

<sup>209</sup> Nerurkar, *Division of Bioequivalence Review*, *supra* note 92.

<sup>210</sup> Fanning, *Medical Officer Review* (Sept. 22, 2000), *supra* note 208 (“The Sponsor has submitted a synopsis of a protocol to study the clinical bioequivalence of their product to the Reference Listed Drug. This is based on the data used to support the approval of the NDA product. Please refer the consult to the Division of Anesthetic, Critical

second inquiry from a different generic sponsor queried whether a bioequivalence study with pharmacokinetic endpoints would be sufficient.<sup>211</sup> The Division of Anesthetic, Critical Care and Addiction Drug Products therefore commented on both the proposed clinical study protocol and the query regarding pharmacokinetics.<sup>212</sup>

Notwithstanding Dr. Nerurkar's appeal to a medical consult as the primary justification for OGD's determination of a chemistry issue, the medical consult report did not in fact make a *determination* that pharmacokinetics were an adequate basis for establishing bioequivalence. The clinician merely opined that, based on his clinical experience, it would "seem appropriate"<sup>213</sup> to use pharmacokinetics, and he deferred to OGD to make a decision about whether clinical endpoint studies would be required.

Dr. Nerurkar offered several additional points as "data" to support his decision to overturn the primary reviewer. First, Dr. Nerurkar claimed that a study with clinical endpoints was "not as discriminatory" as a pharmacokinetic study.<sup>214</sup> As discussed above, FDA regulations do not enshrine discrimination as the singularly relevant factor in determining the most appropriate bioequivalence method. Rather, as made painstakingly clear in the DPK deliberations, sensitivity must be carefully balanced with whether a method is discriminating according to clinical relevance.

Second, Dr. Nerurkar claimed that a pharmacokinetic study provided "a robust comparison of formulations."<sup>215</sup> However, Dr. Nerurkar failed to provide any actual data to support how pharmacokinetic measurements provided a "robust comparison" of topical products for which the active ingredients were only minimally detectable in plasma. In particular, he failed to identify even a single study that directly assessed whether pharmacokinetic measurements related to local concentrations of lidocaine and prilocaine.

Third, Dr. Nerurkar identified two locally acting delayed release oral tablets for which OGD required pharmacokinetic rather than clinical studies. However, Dr. Nerurkar did not relate how OGD's decision to accept pharmacokinetic studies for locally acting GI products, even if scientifically justified, related to the supposed ability of pharmacokinetic measurements to reflect bioavailability at sites of action in the dermis.

Finally, Dr. Nerurkar stated that OGD "requests a bioequivalence study with clinical end points when i) no other properly validated study is possible (e.g. antifungal topicals) or ii) [a] drug

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Care, and Addiction Drug Products (HFD-170) so they can comment on the appropriateness of the study proposed to determine the bioequivalence of the generic and innovator drug product.").

<sup>211</sup> Rappaport Memorandum, *supra* note 208 (stating that the Division of Anesthetic, Critical Care and Addiction Drug Products received two separate consultations from OGD); Fanning, *Medical Officer Review* (Oct. 10, 2000), *supra* note 208 (referencing two inquiries submitted to the Division of Anesthetic, Critical Care and Addiction Drug Products).

<sup>212</sup> See Rappaport Memorandum, *supra* note 208; Fanning, *Medical Officer Review* (Oct. 10, 2000), *supra* note 208.

<sup>213</sup> Rappaport Memorandum, *supra* note 208.

<sup>214</sup> Nerurkar, *Division of Bioequivalence Review*, *supra* note 92.

<sup>215</sup> *Id.*

warrants a bioequivalence study with clinical end points (clozapine).”<sup>216</sup> Dr. Nerurkar further stated that the topical product under review did not fit either of those two categories. However, Dr. Nerurkar’s statement seems to support Dr. Shrivastava’s position that a clinical endpoint study was required, because there was no evidence of a “properly validated study” other than a clinical endpoint study for demonstrating bioequivalence to EMLA. Further, it shows a lack of understanding by Dr. Nerurkar of the issues under consideration. Clozapine, an important antipsychotic drug associated with serious adverse events, was the subject of multiple Advisory Committee meetings and Guidance documents. At no point were clinical endpoint studies recommended or used in the approval of a clozapine ANDA. It is revealing that OGD management misrepresented several “facts” used as the “scientific justification” for overruling their own primary reviewer.

The lack of data to support Dr. Nerurkar’s decision to overrule Dr. Shrivastava is particularly glaring given the timing of OGD’s review. Dr. Nerurkar signed his review on February 24, 2003.<sup>217</sup> Four days later, on February 28, OGD’s Barbara Davit initialed, on behalf of Dr. Dale Conner, OGD’s Director of Bioequivalence, that Dr. Conner concurred with Dr. Nerurkar and thus did not agree with Dr. Shrivastava.<sup>218</sup> Two weeks later, on March 12, 2003, Dr. Shrivastava recorded that he “DOES NOT CONCUR” with OGD’s final approval of the bioequivalence study.<sup>219</sup>

On March 12, 2003, the same day as Dr. Shrivastava’s objection and two weeks after Dr. Davit initialed Dr. Conner’s concurrence, Dr. Conner publicly stated that there were no data to support using pharmacokinetic tests for topical bioequivalence:

Plasma concentrations, at least in our current way of understanding, are not suitable for looking at drug availability at the site of activity. Now, if we really developed this idea and got a lot more data, our ideas may change in this area, but at our current level of understanding, it just doesn’t really look like a good approach.<sup>220</sup>

There does not seem to have been any valid basis to overturn Dr. Shrivastava when OGD’s Director of Bioequivalence was publicly reaffirming the bases for Dr. Shrivastava’s analysis and directly contradicting the “precedent” Dr. Nerurkar identified as controlling.

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<sup>216</sup> *Id.*

<sup>217</sup> *Id.*

<sup>218</sup> *Id.*

<sup>219</sup> *Id.*

<sup>220</sup> Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 183.