

B

## **Appendix B. Evaluation and Withdrawal of Draft Guidance for Topical Product Bioequivalence**

OGD formally proposed a DPK test as a universal method for demonstrating topical bioequivalence in June 1998 and withdrew the draft guidance four years later in May 2002 as it became apparent that the proposed DPK test did not correlate with clinical effects at local sites of action. During numerous advisory committee discussions of OGD's proposed method, scientific experts highlighted a variety of issues that questioned whether approaches other than comparative clinical endpoint studies could reliably establish bioequivalence for topical products. Although these issues were raised in the context of a skin stripping test, they are equally applicable to assessing whether pharmacokinetic tests could reliably be used to demonstrate bioequivalence for topical products.

*OGD Proposed the DPK Method Despite Early Warnings About its Capacity to Correlate with Relevant Clinical Effects.*

OGD was aware of significant concerns about the DPK method before it issued its draft DPK Guidance in 1998. To its credit, OGD pursued an open public process in proposing DPK as an alternative bioequivalence method. This helped ensure that the DPK approach to bioequivalence was proposed and considered in a manner consistent with open public process and sound science.

One of the most critical concerns about DPK related to its ability to correlate with *in vivo* efficacy at the site of action. For instance, a report from a May 1989 joint workshop of FDA and the American Association of Pharmaceutical Scientists ("AAPS") highlighted the challenge of correlating stratum corneum concentrations with any particular target area of the skin:

The correlation between the amount of drug in the stratum corneum and total drug absorption has only been established for some drugs and formulations. Since different body sites of skin have different drug penetration properties, the site of application has to be specified for predicting drug absorption like for any other method. This method does not sample the epidermis or the dermis (i.e., the normal 'targets' of topical drug products).<sup>158</sup>

A 1996 AAPS workshop report again highlighted the challenge of correlating DPK with clinical effect and cautioned OGD that scientific validation and correlation with clinically relevant effects were prerequisites for implementing the method:

Before a DPK method is adopted as a basis for bioequivalence, it must be shown that the differences in DPK capture or reflect significant clinical[ly] important differences in formulations.<sup>159</sup>

---

<sup>158</sup> Quoted in Johnson & Johnson, Comments on FDA's *Topical Dermatological Drug Products Draft Guidance* (Aug. 17, 1998), Docket No. 98D-0388, at 1 (attached as Ex. 16).

<sup>159</sup> Quoted in Jonathan Wilkin, M.D., Presentation at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 64.

Despite the fundamental concerns about validation and correlation with clinical efficacy, OGD published draft Guidance in June 1998 that proposed the DPK method without significant change from earlier protocols. In brief, OGD presented DPK as a measure of drug concentration in the skin as a function of time to compensate for the limitations of measuring drug concentration in biological fluids and correlating such measurements to bioavailability at the site of action. Drug concentrations would simply be measured in the stratum corneum rather than biological fluids.<sup>160</sup>

The Guidance acknowledged that the stratum corneum was not actually the site of action.<sup>161</sup> However, because topical products had to pass through the stratum corneum to get to the epidermal and dermal layers, OGD argued that “the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed.”<sup>162</sup> Moreover, OGD proposed that “DPK principles should be generally applicable to *all topical dermatological drug products* including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products.”<sup>163</sup> Consequently, OGD hoped that DPK could become the primary method of demonstrating bioequivalence for all topical dermatological products.<sup>164</sup>

*FDA Advisory Committee Discussions of OGD’s Proposed DPK Method Emphasized the Complexity of the Skin and the Importance of Correlating Bioequivalence Methods with Clinical Effects.*

Scientific experts identified numerous problems with OGD’s proposed DPK method, which were repeatedly flagged at FDA advisory committee meetings both before and after issuance of the draft DPK Guidance. FDA’s Director of the Dermatological and Dental Drug Products Division, Dr. Wilkin, became a leading and persistent critic of the DPK method as he discussed a “catalogue of concerns.”<sup>165</sup> Criticisms voiced at advisory committee meetings indicated that OGD had once again become susceptible to a “naïve view” of the skin and topical products:

“Skin” vs. Stratum Corneum. OGD’s nomenclature for DPK was misleading. “Dermatopharmacokinetics” implied pharmacokinetic measurements in *skin*. However, the DPK method actually measured drug concentration in the stratum corneum, which, as Dr. Wilkin put it, “at least to dermatologists, is not the same thing as skin.”<sup>166</sup> OGD eventually clarified that it was measuring drug concentration in the stratum corneum rather than the skin itself.<sup>167</sup>

---

<sup>160</sup> TOPICAL DERMATOLOGICAL DRUG PRODUCTS DRAFT GUIDANCE, *supra* note 57, at 4 (“The dermatopharmacokinetic (DPK) approach is comparable to a blood, plasma, urine PK approach applied to the stratum corneum. DPK encompasses drug concentration measurements with respect to time and provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration-time curve.”).

<sup>161</sup> *Id.* at 5.

<sup>162</sup> *Id.*

<sup>163</sup> *Id.* (emphasis added).

<sup>164</sup> *Id.*

<sup>165</sup> Jonathan Wilkin, M.D., Remarks at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 6486, at 45.

<sup>166</sup> Jonathan Wilkin, M.D., Remarks at DODAC Meeting (Mar. 19, 1998), *supra* note 57, at 110.

<sup>167</sup> Compare Vinod P. Shah, Ph.D., slide from Presentation at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 86 (“Pharmacokinetics applied to drug concentration measurements in stratum corneum (SC) is termed DPK.”), with Vinod P. Shah, Ph.D., slide from 1998 presentation, reproduced in Jonathan Wilkin, M.D., Presentation at

Role of Vehicle/Excipients. Excipients in topical products can have significant effects even as and after the drug substance reaches the site of action. Although OGD did not give any special consideration to the role of excipients in its June 1998 draft Guidance, in October 1998 OGD acknowledged that “inactive ingredients can contribute to the overall clinical effect” and indicated a willingness to take this factor into account.<sup>168</sup> In 2000 OGD proposed to apply DPK only to generic products for which the inactive ingredients demonstrated qualitative and quantitative sameness within +/- 5% instead of +/- 10%.<sup>169</sup>

Differential Performance of Concentrations in the Skin. Drug products present in comparable concentrations in the stratum corneum do not all behave the same after penetrating the stratum corneum. The thermodynamic activity on one side of the absorption process affects what happens once the drug makes it into the stratum corneum. The vehicle therefore has a far-reaching impact.<sup>170</sup>

Lack of Data. While many advisory committee members suggested DPK might well prove useful for some drug products, many also viewed the Guidance as premature because OGD lacked sufficient data to support its claims.<sup>171</sup> Even after OGD withdrew its draft Guidance, it was noted that, despite the longstanding debates, “DPK is a relatively new method, and it really hasn’t had time to mature and be fully developed.”<sup>172</sup>

Multiple Pathways. The skin presents multiple pathways to various potential sites of action.<sup>173</sup> Although some products may be absorbed sequentially through the stratum corneum, epidermis, and dermis, drug products may also reach sites of action through follicular pathways and perhaps even through sebaceous glands. Consequently, measurements of drug concentration in select strips of stratum corneum do not reflect drug products’ various preferences among pathways into the skin.<sup>174</sup>

Multiple Target Sites. Despite OGD’s claim that “there is always a clear cut correlation between what is in the horny layers, versus what is in the epidermis and the dermis,”<sup>175</sup> various drug products have distinct targeted sites of action within the skin. Stratum corneum concentrations, even if reliably measured, do not necessarily correlate with availability of drug at sites of action in the skin.<sup>176</sup>

---

DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 64 (“What is Dermatopharmacokinetics? Kinetics of the drug in the skin; Pharmacokinetics applied to the skin.”).

<sup>168</sup> Roger L. Williams, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 16.

<sup>169</sup> Background Briefing, ACPS/DODAC Meeting (Nov. 17, 2000), available at <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3661b1b.pdf>.

<sup>170</sup> Efraim Shek, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 248.

<sup>171</sup> Richard Guy, Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 169.

<sup>172</sup> Annette L. Bunge, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 168.

<sup>173</sup> *See, e.g.*, Jonathan Wilkin, M.D., Remarks at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 86, at 97 (“The skin is composed of a lot of different components. It really is not just Saran wrap covering human beings. It’s got a lot of different pieces to it. There are different ways that topical products get to those sites of action.”).

<sup>174</sup> Jonathan Wilkin, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 111; Richard Guy, Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 174.

<sup>175</sup> Hans Schaefer, Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 42.

<sup>176</sup> Dr. Philip Lavin, Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 107; Jonathan Wilkin, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 110.

Lack of Correlation with *In Vivo* Effects. Consistent with early warnings about the need for correlation, advisory committee members continued to caution OGD that the DPK method should not be used unless actually correlated with *in vivo* effects. This was particularly important if OGD aimed to use DPK to replace comparative critical trials rather than supplement them. OGD acknowledged that “[r]elevance to clinical efficacy” was a critical factor in determining whether OGD could have confidence in the DPK method. Specifically, it was important to determine whether DPK could “differentiate products with [the] same concentration of active [ingredients] but with different clinical efficacy.”<sup>177</sup>

Advisory Committee members felt OGD failed to establish a correlation with clinical efficacy that could justify supplanting use of clinical endpoint studies to establish bioequivalence. For instance, Advisory Committee member Lynn Drake, M.D., stated:

I think this [DPK method] is very risky because . . . [w]e are talking about throwing out the standard reviews for years and years of clinical research, I mean of looking at patients and the effect of drugs on patients, and there isn't a person in this room that doesn't understand there is a difference in vehicles, there is a difference in particle size. There are so many variables, that to throw that out with as little validation as we have, I think it is a mistake and I don't see how we can answer [the applicability of DPK to particular drug product classes] because we haven't seen the validation data by which to base our opinions.”<sup>178</sup>

Inequivalence of Supposedly Therapeutically Equivalent Products. As the experience with topical corticosteroids shows, products designated as bioequivalent by OGD are not necessarily therapeutically equivalent in practice. As John DiGiovanna, M.D., special government employee consultant for DODAC, stated:

Doctor Shah, you refer to these inactive ingredients and it's difficult for us dermatologists to express how we feel when we hear that. Many of us have used preparations that are listed as generic equivalents and many dermatologists will tell you such and such preparation doesn't work and it may be listed as equivalent.<sup>179</sup>

Impact of Diseased Skin. There is considerable variability in predictive value between diseased and normal skin<sup>180</sup> because damaged skin does not behave the same as healthy skin in terms of absorption and permeability.<sup>181</sup>

---

<sup>177</sup> Vinod P. Shah, Ph.D., Presentation at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 86.

<sup>178</sup> Lynn Drake, M.D., Remarks at DODAC Meeting (Mar. 19, 1998), *supra* note 57, at 121.

<sup>179</sup> John DiGiovanna, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 156-57.

<sup>180</sup> *Id.* at 85-86.

<sup>181</sup> Jonathan Wilkin, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 116-17.

Impact of Repeated Applications. Repeated application of topical products can yield changes in metabolic activity and permeability, thereby changing the amount of drug available at the site of activity.<sup>182</sup>

Sensitivity versus Accuracy. Although proponents of DPK regarded the assay as highly *sensitive* and reproducible, advisory committee members emphasized that other methods could in fact be more *accurate*.<sup>183</sup> Being sensitive or discriminatory was not necessarily predictive of efficacy or clinically relevant.<sup>184</sup> Dr. Drake explained:

I am unwilling as one member . . . to accept this test as a replacement for what we actually do in patients and see in patients. . . . [A]s far as I am concerned, [this test] is still way far away from me being able to accept it as the best way to evaluate or accept judgment on [an] equivalent drug.<sup>185</sup>

Similarly, Dr. Wilkin asserted that clinical trials currently provide the most meaningful assessment of efficacy and that the sensitivity and specificity of the assay should be evaluated relative to clinical data: "I will grant that the clinical test is an imprecise answer . . . , but it is an imprecise answer to what I think most clinicians, at least, think is the right question."<sup>186</sup>

Indiscriminate Application of a Single Test. OGD proposed to use the DPK method uniformly for *all* topical products. However, such an indiscriminate application of this method belied basic anatomy. The vaginal mucosa, for instance, does not even *have* a stratum corneum. Notwithstanding the obvious challenges for performing a skin stripping method on vaginal mucosa, it gave one pause that OGD would propose using a bioequivalence test that depended upon a non-existent anatomical structure. In 2000, OGD proposed removing vaginal products from the range of products that would be subject to the DPK method.<sup>187</sup> However, advisory committee members explained it was still inappropriate to use stratum corneum concentrations uniformly without demonstrating correlation to specific regions in the skin for particular drug products.

Lack of Equilibrium State. Topical drug products do not reach an equilibrium state. Although OGD characterized the stratum corneum as a "reservoir," an equilibrium state is not attained and the vehicle of the drug product may continue to affect performance of the active ingredients at the site of action in the skin.<sup>188</sup>

Absence of Predictive Value. Arthur H. Kibbe, Ph.D., recounted the basic assumptions of the DPK as analogizing to pharmacokinetics, that if a drug gets into the stratum corneum DPK can predict what will be available at the site of action. "What I see with a topical is

---

<sup>182</sup> Jonathan Wilkin, M.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 219.

<sup>183</sup> Joel Mindel, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 99-100.

<sup>184</sup> John DiGiovanna, M.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra* note 85, at 103-04.

<sup>185</sup> Lynn Drake, M.D., Remarks at DODAC Meeting (Mar. 19, 1998), *supra* note 57, at 139.

<sup>186</sup> Jonathan Wilkin, M.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 250.

<sup>187</sup> Background Information, DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 86.

<sup>188</sup> Jonathan Wilkin Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 216-220.

that the nature of the vehicle will impact the other things. I am not so sure that we are on as safe a ground using that kind of a measure as we are when we look at blood levels.”<sup>189</sup>

**Reproducibility.** The DPK method suffered from disparate laboratory testing that showed contradictory rather than merely inconsistent results. Validation that a reproducible test accurately measured the rate and extent of absorption of drug at the sites of action was not demonstrated. Although OGD devoted considerable energy to trying to increase the reproducibility of the DPK method, other problems identified above presented “core” issues that would not be resolved simply by having a more reproducible method.<sup>190</sup>

*OGD Withdrew its Draft DPK Guidance Because the DPK Method Was Neither Reproducible Nor Capable of Correlating with and Predicting Relevant Clinical Effects.*

Throughout the advisory committee meetings regarding the proposed DPK method, various participants and public commentators recommended withdrawal of the draft Guidance.<sup>191</sup> By 2001 it became clear that the concerns about DPK were likely insurmountable and an advisory committee meeting featured a discussion of whether OGD should simply cut its losses and go back to the drawing board.<sup>192</sup> Although DPK proponents continued to insist that DPK was a reliable method,<sup>193</sup> notwithstanding study results that contradicted recognized clinical results, the advisory committee offered little support for finalizing the Guidance.<sup>194</sup>

OGD withdrew its draft DPK Guidance in May 2002, but with little explanation.<sup>195</sup> OGD acknowledged that the information and comments it received through public comment and the

<sup>189</sup> Arthur H. Kibbe, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 202.

<sup>190</sup> Jonathan Wilkin, M.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 213.

<sup>191</sup> See, e.g., Jonathan Wilkin, M.D., Presentation at DODAC/ACPS Meeting (Nov. 17, 2000), *supra* note 64 (offering “[T]he Case Against Using DPK Now to Document BA/BE for Topical Drug Products”).

<sup>192</sup> Meeting of the Advisory Committee for Pharmaceutical Science (Nov. 29, 2001) [hereinafter ACPS Meeting (Nov. 29, 2001)] (transcript available at [http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2\\_01\\_Morning\\_Session.pdf](http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2_01_Morning_Session.pdf) and [http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2\\_02\\_Morning\\_Session.pdf](http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3804t2_02_Morning_Session.pdf)).

<sup>193</sup> Lynn K. Pershing, Ph.D., Remarks at ACPS Meeting (Nov. 29, 2001), *supra* note 192, at 40 (“In summary, DPK is a good method for bioequivalence assessment of topical drug products. It’s objective. It’s sensitive. It’s discriminating. It’s precise, accurate. Most importantly, it’s scientifically and clinically relevant. And it’s comparable to pharmacokinetic methods used for oral solid dosage forms. In conclusion, then, DPK results predict the clinical efficacy and safety results. DPK is a sensitive, reproducible, and valid method for bioequivalence assessment of topical drug products.”).

<sup>194</sup> See, e.g., ACPS Meeting (Nov. 29, 2001), *supra* note 192, at 90 (observing how “two different labs doing quite reputable, representative work” to validate DPK “c[a]me up with absolutely opposite responses,” and stating, “The jury is still out in my mind. I don’t think we’ve got a robust test.”) (Remarks of Arthur H. Kibbe, Ph.D.); *id.* at 101 (“So I think we have a choice of leaving this guidance that is of questionable, broad application on the books or withdrawing it. And at some point in time, with further research, sponsored by whoever, bring it back. There’s nothing wrong with taking something back and then getting more data and bringing it forth again, is there? I mean, that’s certainly a viable approach.”) (Remarks of Marvin C. Meyer, Ph.D.); *id.* at 104 (“I don’t think this is a viable method. I don’t think we can go back and collect the data that we would really need . . . because my issue is that I can’t link what you’re testing to clinical endpoints, which presumably we are trying to predict in terms of therapeutic substitution.”) (Remarks of Jurgen Venitz, M.D., Ph.D.); *id.* at 106 (“I would agree with the comments that have been made. It’s not a viable approach at this time.”) (Remarks of Judy Boehlert).

<sup>195</sup> Notice of Withdrawal, Draft Guidance for Industry on Topical Dermatological Drug Product NDAs and ANDAs, 67 Fed. Reg. 35122 (May 17, 2002).

advisory committee meetings “raised scientific concerns” about the DPK method.<sup>196</sup> In particular, “substantial doubt” was raised about whether the DPK method could determine bioequivalence for topical products that targeted sites of action outside the stratum corneum and whether the method could be reproduced in different laboratories.<sup>197</sup> OGD indicated that it would continue to develop alternative methods for establishing bioequivalence for topical products. In March 2003, Dr. Conner emphasized that the DPK method’s correlative value was central to the decision to withdraw the Guidance:

There was limited, if any, relation to drug availability at the site of activity. So we didn’t really have a great correlation to the actual drug appearance at the site of activity.<sup>198</sup>

---

<sup>196</sup> *Id.* at 35123.

<sup>197</sup> *Id.*

<sup>198</sup> Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 182.