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**Supplemental Submission
in Support of Citizen Petition and Petition for Stay
Docket Nos. 2004P-0140/CP1 and 2004P-0140/PSA 1**

On behalf of King Pharmaceuticals, Inc., (“King”) the undersigned hereby make this supplemental submission in support of the above-referenced Citizen Petition and Petition for Stay.

I. Communications Between FDA and Elan In 2002 Confirm the Need for the Clinically-Determined Food Effect with SKELAXIN® to be Reflected in Product Labeling

Included as attachments to this supplemental submission are three communications between FDA and Elan Pharmaceuticals, Inc. on June 7 and 11, 2002, concerning modification of the SKELAXIN® Package Insert language that originally appeared in the Agency’s May 31, 2002 supplemental approval letter. The first of these attachments, dated June 7, 2002, followed a June 6, 2002 telephone conference meeting

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between Elan and the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. That letter states:

We understood from yesterday's discussion that the Agency was in broad agreement with the information contained within our submission dated April 25, 2002, with the caveat that the Agency would like Elan to propose some language to relate the PK findings to the possible clinical relevance, although it was mutually acknowledged that there [are] no clinical data available that could provide *specific* guidance.

See Letter to FDA (June 7, 2002), attached hereto as Exhibit 12 (emphasis added)¹. The June 7 letter then went on to propose specific revised language for the Pharmacokinetics section of the SKELAXIN® labeling. Thereafter, FDA proposed a further revision to this section. See Facsimile to Elan (June 11, 2002), attached hereto as Exhibit 13. Elan accepted this version by letter on that same day. See Letter to FDA (June 11, 2002), attached hereto as Exhibit 14, and it was approved in FDA's letter of June 20, 2002. See Exhibit 3 to King's March 18, 2004 Citizen Petition.

These communications confirm that the June 20, 2002 supplemental labeling revision was based on the belief, held by both Elan and FDA, that the available clinical data did not, at that time, warrant a specific dosing recommendation with respect to food. The communications also confirm, however, that neither FDA nor Elan believed or argued that the PK findings lacked clinical relevance or were not necessary to include in the Package Insert.

¹ To avoid duplication of exhibit numbers used in the Citizen Petition, the exhibits to this Supplemental Submission are designated Exhibits 12 through 16.

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II. The April 6, 2004 FDA Decision on the Ribavirin Petition Underscores FDA's Limited Authority to Permit Label Carve-Outs Only When Omitted Information Does Not Bear On The Safety and Effectiveness of a Drug For Its Labeled Uses

As we pointed out in our March 18, 2004 Petition, King does not dispute that FDA has the authority to permit ANDA applicants to carve out labeling pertaining to patented or exclusive uses of pioneer products, as long as the omitted labeling does not bear on the safe and effective use of the generic products for the indications and conditions of use that remain in the generic labeling. For instance, in the case of ANDAs for generic ribavirin products, FDA has recently concluded that labeling about the patented use of ribavirin with a newer version of interferon may be carved out of the current labeling approved for the reference listed drug, because the omission of that information does not affect in any way the safety and effectiveness of the drug in its non-exclusive and non-patented use with an older version of interferon. In reaching that conclusion, however, the agency reaffirmed that:

. . . FDA may approve an ANDA for a proposed ribavirin capsule drug product, provided that the labeling differences (due to the fact that information is protected by patent or exclusivity) do not render the generic ribavirin capsule drug product less safe or effective than Rebetol Capsules for "all remaining, non-protected conditions of use." Accordingly, the relevant question is whether a generic ribavirin capsule drug product, when labeled to exclude protected information (e.g., information on the use of ribavirin capsules in combination with PEG-Intron), will be rendered less safe or effective than Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A.

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See Letter from Steven K. Galson, MD, MPH, to David M. Fox, Esq. Docket No. 2003P-0321 (April 6, 2004), page 18, attached hereto as Exhibit 15. FDA then pointed out that the safety and effectiveness issues raised in the ribavirin petition related solely to the potential use of the generic ribavirin products for the use that was proposed to be carved out of the labeling, *i.e.*, use with PEG-Intron. On this basis, FDA concluded that the issues raised did not call into question the safety and effectiveness of the generic ribavirin products for use with the Intron-A product because all relevant information on that use would remain in the generic labeling. Based solely on the nature of the information to be carved-out, and a logical analysis of the relevance of that information to the remaining conditions of use, there was no need for FDA to conduct a medical or scientific analysis of the impact of the proposed omission or to require the generic applicants to provide data to back up the view that the omission would have no impact on the safety and effectiveness of the generic products for the remaining labeled uses. Thus, the permitted carve-out of ribavirin labeling was regarded by FDA as completely consistent with previous examples of permitted labeling carve-outs – citing the exclusion of protected dosing schedules from labeling of generic tramadol products and the exclusion of indications with indication-specific dosing instructions. *See*, Exhibit 15, page 20.

In contrast, the proposal to carve-out pharmacokinetics information which clearly pertains to the labeled indication for use of generic metaxalone products directly raises medical and scientific questions never before addressed by FDA or generic applicants in

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this context. As we pointed out in the March 18, 2004 Petition, it is scientifically irresponsible and legally indefensible to accept on faith the assertion by any generic applicant that information about the pharmacokinetics of their products in oral administration has no bearing on the safety and effectiveness of those products. Such an assertion flies in the face of long-standing FDA labeling requirements applicable to all prescription drugs and directly contradicts the FDA's own recent decisions to require both fed and fasting bioequivalence tests of metaxalone products.² If generic applicants are not required to provide adequate clinical data to prove that assertion, then the requirement that label carve-outs not impair the safety or effectiveness of their products for their labeled uses would be rendered a nullity. Where, as here, there are clear, undisputed medical and scientific bases for concern about the relevance of the known pharmacokinetics of metaxalone to the use of the product in oral administration, it is the burden of those who would omit that information from their labels to provide data proving that the information is truly irrelevant to the safety and effectiveness of their

² In this regard, we point out that FDA has never permitted an ANDA applicant to carve out labeling information pertaining to the pharmacokinetics of a drug in oral administration when the generic drug would nevertheless be indicated for oral administration. To the contrary, even when available pharmacokinetics information pertains to dosage forms or strengths which the applicant does not propose to sell (and cannot sell because of exclusivity restrictions), FDA has required generic labeling to include all pharmacokinetic information that appears in the labeling of the reference listed drug. *See* Package Insert for Teva's 80 mg oxycodone hydrochloride extended release tablets, approved by FDA on March 23, 2004, attached hereto as Exhibit 16.

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products for their labeled uses. *See* Section II.C.2. of Citizen Petition; 21 U.S.C. § 355(j)(2)(A)(v); 5 U.S.C. § 556(d); 21 C.F.R. § 12.87(d).

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'P. Mathers', written in a cursive style.

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