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VIA FEDERAL EXPRESS

May 16, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket Number 02P-0406, Comments

On September 10, 2002, THE WEINBERG GROUP INC. submitted a suitability petition ("the Petition") requesting the Commissioner of FDA to declare that the drug products Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension 200 mg/28.5 mg, 400 mg/57 mg and 600 mg/42.9 mg were suitable for submission as an Abbreviated New Drug Application (ANDA). The only change being sought in the Petition is that of a change in the dosage form. The proposed Tablets for Oral Suspension products are not intended to be therapeutically equivalent ("AB rated") substitutes for the GSK Augmentin products but are intended to be pharmaceutical alternatives where a Tablet for Oral Suspension may be a preferred therapeutic modality as determined by an appropriate medical professional.

In response to the petition, on December 19, 2002, Hogan & Hartson L.L.P. submitted comments to the petition. In summary, these comments incorrectly allege that the Petition requests more than a change in dosage form by wrongly asserting that the Petition further requests changes in strength, approved dosing regimen and conditions of use. The Hogan & Hartson comments further allege that the term "tablets for oral suspension" is not currently

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recognized within the Agency's nomenclature. Finally, the Hogan & Hartson comments purport to raise numerous safety concerns that are either inaccurate or not applicable. According to the Hogan & Hartson comments, these changes would require "extensive changes to the approved labeling and raise significant questions of safety and effectiveness" and consequently ask that the Petition should be denied. As described in greater detail below, the petitioner completely disagrees with this characterization of the change requested in the Petition.

Response to Comments

There is No Change in Strength

The Hogan & Hartson comments allege that the Petition seeks a change in strength. In fact, there is no change in strength being sought in the Petition. The Petition has been submitted only for a change in the dosage form from "Powder for Oral Suspension" to "Tablet for Oral Suspension." In both of these dosage forms (i.e., proposed product and reference product), the strength in terms of amoxicillin content and clavulanate potassium content is precisely the same; namely, powder for oral suspension, 200 mg/28.5 mg, 400 mg/57 mg and 600 mg/42.9 mg per 5 ml; and tablets for oral suspension, 200 mg/28.5 mg, 400 mg/57 mg and 600 mg/42.9 mg per tablet. The dosing unit of the reference product (5 ml) **(Attachment 1)** and of the proposed product (tablet) contains identical amounts of the active ingredients.

The Hogan & Hartson comments also attempt to show that the strength is changed because the concentration of the administered suspension may be different. The Hogan & Hartson comments characterize 21 CFR 210.3(b)(16)(i) in support of this notion by stating that the regulation "define[s] strength to mean, in relevant part, concentration of the drug based on weight/volume[.]" However, this citation taken out of context, neglects to include the complete regulation, which states that strength also is defined by potency as follows:

> Strength means: (i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or

> (ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

21 CFR 314.93(b)(16)(i) (emphasis added).

Based on this preferred definition of strength, the 200 mg, 400 mg, and 600 mg tablets for oral suspension have the same strength as the reference product. The Hogan & Hartson comments fail to explain why it is reasonable to assume that its selectively quoted definition of strength is more applicable to the 600 mg tablets for oral suspension for amoxicillin and clavulanate potassium than the definition contained in the unquoted portion of the regulation. Furthermore, SmithKline Beecham, a unit of GSK, sells an Augmentin tablet for oral suspension in Europe as Augmentin Dispersible Tablets. In fact, the reference product's labeling for this product in Europe (see **Attachment 2**) requires the tablet to "be stirred in a little water," creating suspensions having varied concentrations based on the individual caregiver's definition of "a little water." This clearly indicates that GSK has no actual concerns about the drug's concentration, and that strength is adequately, if not preferably, defined by potency. Its own labeling demonstrates that GSK uses potency as the measure of strength for their dispersible tablets for oral suspension for amoxicillin and clavulanate potassium. Thus, THE WEINBERG GROUP believes that there is no real misunderstanding about the strength remaining unchanged.

There is No Change in Dosing Regimen

The Hogan & Hartson comments allege that the Petition seeks a change in the dosing regimen. In fact, a change in dosing regimen is not sought. The labeling for the reference product, Augmentin ES-600™, directs the caregiver to administer the proper amount of the drug to the patient based on the weight of the patient as does the proposed labeling in the Petition. Specifically, the 200 mg tablet for oral suspension is appropriate only for a 200 mg dose, the 400 mg tablet for oral suspension is appropriate only for a 400 mg dose and the 600 mg tablet for oral suspension is appropriate only for a 600 mg dose.

With its unchanged dosing regimen, the proposed product provides increased ease of use. It is important to recognize that the main purpose of the proposed product is to provide an

alternate dosage form that will enable ease of use without compromising safety and effectiveness. The labeling will instruct patients to consume the entire dose as prescribed. Thus, the proposed product is targeted only for that population of patients in which a full-tablet, or multiples thereof, are recommended. For example, Verispan's Physician Drug and Diagnostic Audit (**Attachment 3**) indicates that of the prescribed dosages of amoxicillin and clavulanate potassium only 22% are prescribed for an intermediate dosage (i.e., 1 and ½ tsp or less than 1 tsp). In view of this historical data, with the exception of the 22% of those for whom an intermediate dose is prescribed, the majority of patients can take advantage of this more convenient dosage form. Moreover, for those instances in the pediatric population in which dose-titration is frequently needed, the existing "powder for oral suspension" dosage form is recommended.

The following information is given in the Patient Information Leaflet of 'Augmentin' Dispersible Tablets marketed in Europe:

-These tablets are usually prescribed for adults and children over 12 years of age.

Although GSK has a powder for oral suspension in the U.S., in Europe GSK has both "Tablets for Oral Suspension" and "Powder for Oral Suspension". The Augmentin powder for oral suspension is recommended for the pediatric population (children up to 12 years of age).

A copy of the Patient Information Leaflet for Augmentin Dispersible Tablets marketed in Europe is in **Attachment 2**.

We do not agree with the Hogan & Hartson position that Augmentin ES-600™ is only approved for a 360 mg (amoxicillin) lowest dose with 180 mg (amoxicillin) increments. The chart that is included in the approved package insert is only a guide to assist health practitioners with the appropriate dose for patients that weigh one of the weights in the chart. However, for patients' with weights other than described in the chart, the dosing of Augmentin ES-600™ is to be based

on the pediatric patient's actual weight and dosed at 90 mg/kg/day divided every 12 hours. This would result in a dosing range between 360 to 1620 mg twice daily. Furthermore, the recommended dose volumes as described in the package insert chart are extremely difficult to measure accurately with a normal teaspoon. It is well known that the volume of teaspoons differ by a great deal[1] and administering the doses as described in the chart without the use of an accurate device such as an oral dosing syringe could result in significant errors of over or under dosing[2].

The petitioner intends to collaborate closely with the Agency on the labeling and package insert of the proposed product to assure the safety and effectiveness of this product. The petitioner also notes that based on past experience with similar dosage forms, the FDA has required statements in the Package Insert, such as, *"The 200 mg Tablet for Oral Suspension is appropriate only for a 200 mg dose. The 400 mg Tablet for Oral Suspension is appropriate only for a 400 mg dose. The 600 mg Tablet for Oral Suspension is appropriate only for a 600 mg dose,''*. Such requirements are completely applicable here and because the Agency is expected to act in a similar manner as it has in similar situations, the concerns raised by Hogan & Hartson will be completely addressed.

There is No Change in the Conditions of Use

The Hogan & Hartson comments allege that the petitioner is seeking a change in the conditions of use of the drug product and that this change would have a negative impact on safety. In fact the Petition does not seek any change in the conditions of use and there is no negative impact on safety. According to the Hogan & Hartson comments, the change in conditions of use allegedly being sought is reconstitution "by a caregiver" as opposed to the reference product's reconstitution "prior to dispensing" by a pharmacist.

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[1] Hyam, E., Brawer,M., Herman, J., Zvieli, S. What's in a teaspoon? Underdosing with acetaminophen in family practice. Fam Pract 1989 Sep;6(3):221-3 **(Attachment 7)**.

[2] Madlon-Kay, D.J., Mosch, F.S. Liquid medication dosing errors. J Fam Pract 2000 Aug;49(8):741-4 **(Attachment 8)**.

The comments speculate, without basis, that the proposed instructions are untested in usage studies. In fact, extensive development studies on the proposed tablets for oral suspension have been conducted and these studies demonstrate that upon placing the tablet in water the tablet disperses into a suspension. Based on these studies, labeling has been prepared that specifies the amount of water in which to disperse the tablet to ensure adequate and immediate dispersion to form the suspension.

The Hogan & Hartson comments raise further illusory concerns, including: (1) the caregiver being unable to recognize "whether they have properly reconstituted the product;" (2) the need for "instruction on whether to discard portions of the reconstituted drug (to achieve a recommended dose);" and (3) "whether unused portions can be saved, and, if so, under what conditions."

GSK's concerns are suspect, given its labeling practices for the analogous product in Europe, for example. Similar formulations of GSK's Augmentin product exist in the European market as 'Augmentin' Dispersible Tablets, marketed by SmithKline Beecham Pharmaceuticals. The tablet is indicated for reconstitution by caregivers, and, according to its labeling (e.g., Patient Information Leaflet) provided in **Attachment 2**, is "usually prescribed for adults and children over 12 years of age." GSK's labeling for its European Augmentin Dispersible Tablets is an implicit acknowledgement by GSK that these concerns are meritless.

Significantly, GSK's labeling for Europe for Augmentin Dispersible Tablets (i.e., tablets for oral suspension) (see **Attachment 2**) gives only the following instruction for dispersing the tablet in water:

> "Each 'Augmentin' Dispersible Tablet should be stirred into a little water before being swallowed."

Similarly, the proposed labeling in the Petition for the proposed product provides the following instructions for the caregiver:

> "Directions for Amoxicillin and Clavulanate Potassium Tablets for Oral Suspension
>
> Dissolve each tablet in 1 tablespoon to 2 ounces of water in a glass, cup or other suitable container. Stir or swirl until a uniform dispersion forms, and drink the entire dispersion. Do not chew or swallow the entire tablets. If tablets are placed in the mouth they will not rapidly dissolve on the tongue."

The lack of any detail in the instructions for use of GSK's European Augmentin product, compared to the far more helpful instructions for use in the proposed labeling demonstrates that there are no new safety and effectiveness problems associated with the proposed product and, therefore, GSK's alleged "concerns" are baseless. Clearly, GSK's European Augmentin labeling does not provide any instruction regarding recognizing "whether they have properly reconstituted the product;" the need for "instruction on whether to discard portions of the reconstituted drug (to achieve a recommended dose);" or "whether unused portions can be saved, and, if so, under what conditions." Because GSK manifestly does not have such concerns for its European customers, and because it is unlikely that GSK is held to a lower standard of safety for its European customers, it should be clear that these fabricated concerns do not have merit. Further, since the rapid dispersion of the proposed tablets for oral suspension shows that the proposed tablets for oral suspension behave similarly to GSK's European Augmentin product, any real concern of GSK is believed to be adequately addressed.

The Labeling Changes will be Adequately Addressed with the FDA

The Hogan & Hartson comments raise concerns about the labeling proposed in the Petition. Contrary to the comments, these issues are suitable for resolution during consultations with the Agency in review of the ANDA. The purpose of the Petition is to seek the FDA's concurrence that the proposed product is suitable as the subject of an ANDA. As required by the regulations (21 CFR § 314.93(d)), the suitability petition must include the proposed labeling. As required by the FDA, the Petition includes the proposed labeling; the final labeling is not provided because the purpose of the Petition is not to finalize the labeling. Nonetheless, the petitioner intends to work closely with the Agency in revising the labeling so that the proposed product is at least as safe and effective as Augmentin. For example, in its consulting with the Agency, the petitioner will take into consideration the labeling of the similar GSK Augmentin sold in Europe, which

has no reported concerns about safety or effectiveness. The petitioner also will review the labeling of reference products having a similar dosage form.

Moreover, the Labeling Review Branch of the Office of Generic Drugs ("OGD") has already worked extensively on the labeling information for the dosage form, "tablets for oral suspension." As per the OGD's requirement, the labeling will be supplemented with a Patient Information Leaflet and "Directions for Use" on the label/labeling. This Patient Information Leaflet will aid in the correct administration of the proposed product. A "Dear Pharmacist" letter also will be included. When supported with FDA-recommended "Directions for Use," the proposed product is even less likely to pose any safety or effectiveness concerns.

In conclusion, once the ANDA is submitted, the petitioner is confident that consultations with the Agency will adequately address the labeling instructions, including recommendations for proper use of this convenient dosage form. Again, the petitioner emphasizes that since the only change requested in the Petition is the dosage form, there are no concerns regarding labeling comprehension, dosing, or safety and therefore clinical investigations are not required.

Dosage form Requested by Petition is recognized by the FDA and by the USP

The Hogan & Hartson comments assert that the Petition's requested dosage form, tablet for oral suspension, is not an FDA-approved dosage form. In support of this, the Hogan & Hartson comments point to the Agency's failure to list this term in Appendix C of the Orange Book and the FDA's requirement in correspondence to THE WEINBERG GROUP that it not use the term "dispersible tablet." The Hogan & Hartson comments specifically characterize a Federal Register notice of February 22, 2001 as stating that Appendix C is informal guidance and that until the dosage form has been added through the appropriate process, the Petition is premature. The Hogan & Hartson comments fail to quote the entire relevant portions of the notice. This notice is being attached to ensure that the Agency has the complete notice (see **Attachment 4**). The petitioner nonetheless wishes to direct the Agency's attention to the following quote from which the Hogan & Hartson quote was snipped:

> [T]he draft guidance refers readers to the Orange Book appendix C, ``Uniform Terms." Although the Orange Book appendix C is not binding on the agency or industry, it does serve as informal guidance on what the ``same" or ``identical" dosage form or route of administration would be.

66 FR 11175, 11175-76 (Feb. 22, 2001) (emphasis added) (see **Attachment 4**).

This passage, far from stating that FDA's guidance process must be used prior to the Agency recognizing a tablet for oral suspension, instead clearly states that the terminology in "appendix C is not binding on the agency or industry[.]"

Moreover, contrary to the assertions, this dosage form and term have been required by the FDA and recognized by the United States Pharmacopoeia ("USP"). For example, the recognition of "Tablets for Oral Suspension", dosage form is obvious from the FDA letter of August 9, 2002, regarding Docket No. 99P-5450/CP1 **(Attachment 5)**. This letter indicates "*The (Labeling and Nomenclature) Committee (of CDER) determined that the optimal nomenclature for this dosage form would be either 'Tablets for Oral Solution' or 'Tablets for Oral Suspension'. The Center (CDER) concurred with this recommendation*". This letter indicates that FDA has already recognized this new dosage form.

Similarly, the USP has already recognized the term "Tablets for Oral Suspension." A draft monograph was proposed for Amoxicillin Tablets for Oral Suspension in the USP Pharmacopoeial Forum, Vol. 28(4) [Jul-Aug 2002], p. 1067. In the briefing of this monograph, the USP indicated the proposal for "Tablets for Oral Suspension" is a new monograph. The proposed monograph of Amoxicillin Tablets for Oral Suspension became official in USP 26, Supplement 1, p. 2942, effective April 1, 2003.

Appendix C of the Orange Book currently lists the dosage form "Tablets for solution" (see **Attachment 6**). Based on the recent recommendation and acknowledgement of this dosage form by USP and the FDA (**Attachment 5**), petitioner anticipates that Appendix C of the Orange Book will be updated shortly by the Agency to include this new dosage form.

The Legal Standard for Approving the Petition is Met

The Hogan & Hartson comments allege that the change proposed in the suitability petition would jeopardize the safe and effective use of the product so as to necessitate significant labeling changes and, therefore, under 21 CFR 314.93(e)(1)(iv) the petition must be denied. To the contrary, for the requested change in dosage form the cited regulation does not require that the FDA deny the Petition.[3] Moreover, any additional information that the FDA requires to ensure safety and effectiveness can be requested at any time during the course of review of the abbreviated application. The Hogan & Hartson comments related to the legal standards for acceptance of a suitability petition are addressed below.

First, the majority of the concerns raised in its comments are either premature or of a nature that is precisely suitable for resolution by the FDA upon approval by the Agency and submission of an ANDA. Specifically, 21 CFR 314.93(e)(3) provides exactly this method for resolution of the concerns raised by Hogan & Hartson. Moreover, this regulation states that the Agency may request additional information as required to properly evaluate the change.

Second, approval of a suitability petition does not guarantee approval of an ANDA. It only gives permission for a company to submit such an ANDA to the FDA for a proposed change.[4] The process of approving a suitability petition involves the scientific staff of the FDA evaluating the petition for new safety and effectiveness concerns beyond those present in the reference drug. In so doing, the applicable regulations at 21 CFR 314.93(e)(3) provide: (1) the Agency may describe what additional information will be required to support an ANDA and (2) during the review of the ANDA, the Agency may request additional information required to further

[3] Petitioner notes that the Hogan & Hartson comments variously describe the petitioner's dosage form as dispersible tablet, tablet for reconstitution, and tablet for oral suspension. To clarify any confusion created by the Hogan & Hartson comments, the petition seeks to use the following term, and only the following term, to describe the drug product: tablet for oral suspension.

[4] A person who wants to submit an abbreviated new drug application for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application. 21 CFR 314.93(b).

evaluate the change.[5] Thus, Hogan & Hartson can be well assured that the Agency will have multiple opportunities to address and resolve the concerns that it has raised in its comments.

For example, Hogan & Hartson raises concerns about the proposed labeling. The applicable regulation, however, requires that a suitability petition include the proposed labeling, not the final labeling.[6] Thus, the concerns about the labeling raised by Hogan & Hartson are exactly the type of concerns that are to be addressed by the FDA during its review of the suitability petition and resolved by requesting, if necessary, additional information from the petitioner.

Conclusion

In conclusion, Hogan & Hartson does not raise any new safety or effectiveness problems, and more so, does not raise any new safety or effectiveness problems that necessitate significant labeling changes. As such, according to the applicable FDA regulations, Hogan & Hartson's comments do not introduce new safety or effectiveness problems that jeopardize the safe or effective use of the product and thus the petition should be approved.

Very truly yours,

Nicholas M. Fleischer, R.Ph., Ph.D.
Vice President, Clinical Pharmacology & Biopharmaceutics
THE WEINBERG GROUP INC.

NMF/kh

Enclosure

cc Gary Buehler, Director, Office of Generic Drugs

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[5] If FDA approves a suitability petition submitted under this section, the Agency's response may describe what additional information, if any, will be required to support an abbreviated new drug application for the drug product. FDA may, at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition. 21 CFR 314.93(e)(3).

[6] The petitioner shall identify a listed drug and include a copy of the proposed labeling for the drug product that is the subject of the petition and a copy of the approved labeling for the listed drug. 21 CFR 314.93(d).