HOGAN & HARTSON

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DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

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Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 02P-0406, Comments

Dear Sir/Madam:

We are writing on behalf of GlaxoSmithKline (GSK) in opposition to the above-referenced petition submitted pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDCA) by The Weinberg Group on September 10, 2002 (the Petition).

GSK markets the approved antibiotic drug products Augmentin® (amoxicillin/clavulanate potassium) Powder for Oral Suspension and Augmentin ES-600™ (amoxicillin/clavulanate potassium) Powder for Oral Suspension. The Petition seeks a declaration that amoxicillin/clavulanate potassium is suitable for submission under an abbreviated new drug application (ANDA) in a "tablet for oral suspension" dosage form.

According to the Petition, the only change being sought is a change in dosage form from that of the reference listed products. In fact, the Petition also seeks a change in strength and a change in the approved dosing regimen. As shown below, this raises significant concerns regarding dosing, labeling comprehension, and safety. Without further investigation and extensive labeling changes, the safety and effectiveness of the products, particularly in pediatric patients, cannot be assured. For those reasons, and because the dosage form requested by the Petition is not currently recognized by the Food and Drug Administration (FDA) or by the

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United States Pharmacopoeia (USP), the Petition must be denied. *See* 21 USC 355(j)(2)(C).

I. BACKGROUND

A. Augmentin® and Augmentin ES-600™

Augmentin® and Augmentin ES-600™ are oral antibacterial combination drug products consisting of amoxicillin and the β-lactamase inhibitor, clavulanate potassium. Augmentin® is approved for use in treating lower respiratory tract infection, otitis media, and sinusitis caused by *Haemophilus influenzae* or *Moraxella catarrhalis*, as well as certain forms of skin infection and urinary tract infection. Augmentin ES-600™ is approved for use in treating pediatric patients with recurrent or persistent acute otitis media due to *Streptococcus pneumoniae*, *H. influenzae*, or *M. catarrhalis*.

Both products are marketed in a powder for oral suspension format, to allow for reconstitution by a pharmacist *prior to dispensing.*[1] Pharmacists are instructed to:

> Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see table below) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

FDA Approved Labeling, "Dosage and Administration" (2002). Patients are advised to shake the oral suspension before use, store the reconstituted suspension under refrigeration, and discard any unused suspension after 10 days. *Id.*

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[1] Augmentin® is also marketed in tablets and chewable tablets; Augmentin ES-600™ is marketed only as a powder. The Augmentin® tablets contain 125 mg of clavulanate and either 250, 500, or 875 mg of amoxicillin. They are recommended for adults and pediatric patients weighing 40 kg and more. The chewable tablets are available in the same strengths as the powder for oral suspension (125, 200, 250, and 400 mg of amoxicillin), and are recommended in the approved labeling "for use by older children." Because The Weinberg Group's suitability petition does not refer to these other dosage forms, we use the name Augmentin® throughout this letter to mean only the powder for oral suspension.

Dosing of the oral suspension is patient-specific, with incremental doses calculated based on the patient's body weight. For Augmentin ES-600™, the labeled dose for pediatric patients 3 months and older is 90 mg/kg/day divided every 12 hours. To ensure accurate calculation of the dose, the Augmentin ES-600™ labeling includes the following chart:

Body Weight (kg)	Volume of Augmentin ES-600 providing 90 mg/kg/day
8	3.0 mL twice daily
12	4.5 mL twice daily
16	6.0 mL twice daily
20	7.5 mL twice daily
24	9.0 mL twice daily
28	10.5 mL twice daily
32	12.0 mL twice daily
36	13.5 mL twice daily

Id. Once the pharmacist reconstitutes the product, each teaspoonful (5 mL) of Augmentin ES-600™ will contain 600 mg of amoxicillin and 42.9 mg of clavulanic acid.

The Augmentin ES-600™ product is marketed in pre-filled 50, 75, 100, and 150 mL bottles for reconstitution by a pharmacist prior to dispensing. The caregiver pours from the bottle only the amount needed for each dose, and each bottle contains the amount needed to complete a full course of therapy.

A similar dosing schedule is approved for use with Augmentin® in 125, 200, 250, and 400 mg strengths (based on the amoxicillin component), and GSK provides pharmacists with three different pre-filled bottle sizes for each approved strength.

Children who receive an excessive amount of Augmentin® or Augmentin ES-600™ may suffer stomach and abdominal pain, vomiting, and diarrhea. Other side effects from inaccurate dosing are described in the "Overdosage" section of the approved labeling.

B. The Proposed Generic Products

According to the draft labeling submitted with the Petition, the proposed generic Augmentin® products will be marketed in 200 and 400 mg tablets for oral suspension, and the proposed generic Augmentin ES-600™ product will be marketed in 600 mg tablets for oral suspension (based on the amoxicillin component). The 200, 400, and 600 mg products will each contain the same ratio of amoxicillin-to-clavulanate as the corresponding reference product.

However, unlike Augmentin® and Augmentin ES-600™, in which the pharmacist is responsible for putting the drug into suspension, the proposed generic is intended to be reconstituted by the caregiver. According to the proposed labeling, the caregiver should dissolve each tablet in "1 tablespoonful to 2 ounces of water," and then "[s]tir or swirl until a uniform dispersion forms." The patient is then instructed to drink the entire dispersion.

For the 600 mg generic product, each *tablespoon* will contain 600 mg of amoxicillin (assuming proper dispersion by the caregiver), as compared to 600 mg per *teaspoon* for Augmentin ES-600™. Because the approved product is intended to be dosed based on teaspoons and fractions of teaspoons, this difference is significant (see discussion below). In addition, the generic product can only be dosed based on full-tablet, 600 mg amoxicillin increments. The reference product, by contrast, can be dosed in 180 mg amoxicillin increments, starting at a dose of 360 mg.

For example, the approved dose of Augmentin ES-600™ for a 20 kg child is 1.5 teaspoons (7.5 mL) every 12 hours or 900 mg of amoxicillin and 64.35 mg of clavulanate. Based on the instructions for the proposed generic, the same child would receive 1 tablespoon every 12 hours or 600 mg of amoxicillin plus 42.9 mg of clavulanate per dose. If the caregiver were instructed to dissolve two tablets, the child would receive 1200 mg of amoxicillin plus 85.8 mg of clavulanate per dose at each 12 hour interval. Neither dose for the generic matches that which has been approved for the reference product.

II. LEGAL STANDARD

Under section 505(j)(2)(C) of the FDCA, "[i]f a person wants to submit an abbreviated application for a new drug which has a different . . . dosage form . . . from that of a listed drug, such person shall submit a petition to the Secretary

seeking permission to file such an application." 21 USC 355(j)(2)(C). The Secretary is instructed to deny the petition – a "suitability petition" – if he finds "that investigations must be conducted to show the safety and effectiveness of the drug or . . . the dosage form . . . which differ[s] from the listed drug . . . ." *Id.* at 355(j)(2)(C)(i).

The phrase "investigations must be conducted" is defined by FDA to mean "that information must be derived from animal or clinical studies" to demonstrate "that the drug product is safe or effective." 21 CFR 314.93(e)(2). In proposing this definition, FDA noted that "[i]f preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an ANDA is not appropriate for the proposed drug product, and FDA will not approve a petition." 54 FR 28872, 28880 (July 10, 1989). In addition, the agency must deny the petition if the proposed change would "jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem . . . ." 21 CFR 314.93(e)(1)(iv).

In short, a proposed change that presents "diminished safety or effectiveness," or would require "heightened labeled warnings" to ensure safe use, must be denied. 54 FR at 28879. The appropriate path for a product that requires additional study or substantial re-labeling is section 505(b) of the FDCA.

III. ANALYSIS

The Petition purports only to seek a change in dosage form. In fact, the Petition also seeks a change in a condition of use (from reconstitution prior to dispensing to reconstitution by a caregiver); a change in strength (*e.g.*, from 200, 400, and 600 mg of amoxicillin per teaspoon to 200, 400, and 600 mg of amoxicillin per tablespoon or per 2 oz.);[2] and a change in the approved dosing regimen (from a starting dose of 360 mg and 180 mg amoxicillin increments for Augmentin ES-600™, to a starting dose of 600 mg and 600 mg amoxicillin increments for the proposed generic). Further, the changes in strength and approved dosing regimen

[2] A tablespoon is approximately 3 times the volume of a teaspoon. On a weight/volume basis, the reference products are at least three times the strength of the proposed generic products. *See* 21 CFR 210.3(b)(16) (defining strength to mean, in relevant part, concentration of the drug based on weight/volume).

represent changes to the corresponding doses of clavulanate administered to the child.

In addition, the dosage form sought in the Petition – tablet for oral suspension or tablet for reconstitution – is not currently recognized within the agency's nomenclature. No standards have been established for such a dosage form and, even more, no studies have been conducted on the labeling and instructions needed to properly use it. Clinical study and careful labeling are needed before this dosage form can be applied to amoxicillin-based products intended for pediatric patients.

A. Dosage Form Issues

The agency's recognized list of pharmaceutical dosage forms is set forth in Appendix C to the FDA publication, "Approved Drug Products with Therapeutics Equivalence Evaluations" (the Orange Book). The list generally tracks the dosage forms described in the general chapters of the United States Pharmacopoeia/ National Formulary. *See* USP 25/NF 18 (2002). While FDA has recognized both powder for reconstitution and granules for reconstitution, as well seven different forms of tablet, the agency has yet to recognize a tablet for reconstitution.

These dosage form categories recognized by FDA represent agency guidance, within the meaning of 21 CFR 10.115, and the agency can add to that list only by following the "good guidance practice" process. *See* 66 FR 11175, 11176 (Feb. 22, 2001) (describing Appendix C as "informal guidance"). Until the dosage form has been added, through the appropriate process, the Petition is premature. Indeed, in response to prior petitions submitted by The Weinberg Group, the agency rejected the petitioner's description of the dosage form as a "dispersible tablet," which is one of the agency's recognized dosage forms. *See* FDA Docket No. 01P-0358/CP1, Letter dated Aug. 9, 2002.

The issue goes beyond nomenclature and process. There are, in fact, no standards in place regarding the use of such a dosage form. For example, the instructions proposed by the petitioner – "stir or swirl until a uniform dispersion forms" – likely have not been tested in usage studies. Caregivers may not recognize whether they have properly reconstituted the product; they may require more guidance, and patient-specific labeling, to ensure proper usage. They also may need instruction on whether to discard portions of the reconstituted drug (to achieve a recommended dose), whether unused portions can be saved, and, if so, under what

conditions. Finally, as discussed below, no standards have been developed regarding the use of "unit dose" tablets for reconstitution in pediatric populations, where much more precise dosing is likely to be required.

In short, the agency must first use its guidance process to recognize a tablet for oral suspension or tablet for reconstitution dosage form. Even then, significant labeling changes would be needed to ensure the safe and effective use of a tablet for oral suspension in pediatric products such as Augmentin® and Augmentin ES-600™. As a result, the Petition must be denied. *See* 21 CFR 314.93(e)(1)(iv).

B. Dosing and Strength Issues

Augmentin® and Augmentin ES-600™ are dosed according to each patient's weight. For example, a 20 kg pediatric patient taking Augmentin ES-600™ requires 900 mg (based on the amoxicillin component), or 7.5 mL of product, twice daily. The use of a powder for oral suspension means the pharmacist can reconstitute enough product for an entire 10 day prescription, allowing the caregiver to measure exactly the right amount (7.5 mL or 1.5 teaspoons) for each dose.

The proposed products, far from providing "[b]etter precision of dosage over the traditional teaspoonful," as the Petition states, rely on the suspension of whole tablets in water and instruct the patient to drink the entire dispersion. In the case of the proposed 600 mg formulation, this means dosing in 600 mg increments only, which is contrary to the approved labeling. The identical 20 kg patient who would receive 900 mg of amoxicillin in 7.5 mL of Augmentin ES-600™ (twice daily) would now receive either 600 mg or 1200 mg of amoxicillin in either one or two tablets of the petitioner's product (plus an increased dose of clavulanate as discussed above).

Nowhere in the proposed labeling are there instructions on whether or how to score the tablets, to enable 180 mg dosing increments (per the Augmentin ES-600™ approved dosing schedule), nor are there instructions on whether or when ***not*** to drink the entire dispersion. As such, the products described in the Petition effectively eliminate the approved dosing increments for Augmentin® and Augmentin ES-600™. For example, the Augmentin ES-600™ product is approved with dosing increments of 360, 540, 720, 900, 1080, 1260, 1440, and 1620 mg of

amoxicillin; the proposed generic would only allow for increments of 600, 1200, 1800, and 2400 mg. Depending on how the caregiver tries to compensate (by using one, two, or three tablets to try to match the approved dose), a child taking the generic will end up under- or over-dosed.[3] The possibility of overdosage is particularly significant here because increased doses of clavulanate are associated with higher incidence of diarrhea.[4]

Finally, even if the caregiver were to reconstitute a tablet, and then measure out a dose according to the Augmentin ES-600™ dosing chart, the dose would be wrong. Based on weight per volume, the strength of the generic is markedly different from the reference product. For example, the Augmentin ES-600™ contains 120 mg of amoxicillin per 1 mL. The strength of the generic varies depending on whether it is dissolved in 1 tablespoon or 2 ounces of water (per the proposed labeling) and, in all cases, is more dilute than the reference product. *See* 21 CFR 210.3(b)(16) (defining strength to mean, in relevant part, concentration of the drug based on weight/volume). Therefore, measuring out a teaspoon of the generic product and a teaspoon of the reference product would not yield the same total dose.

C. Labeling Issues

The Petition oversimplifies the extent of the changes being sought. It seeks permission to use a new dosage form but, importantly, it also seeks (without petitioning) to switch patients to "unit dosing." Unit dosing, however, is incompatible with products that require patient-specific dosing.

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[3] FDA has repeatedly acknowledged the differences between adult and pediatric pharmacokinetics and the importance of pediatric-specific dosing. The elimination of intermediate dosing intervals in the proposed product threatens the safety and effectiveness of a product dosed according to body weight. *See, e.g., Draft Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products* 2-4 (November 1998) (detailing the differences between adults and children in, among others, absorption, distribution, metabolism, and excretion).

[4] *See* Scott F. Dowell et al., *Acute Otitis Media: Management and Surveillance in an Era of Pneumococcal Resistance – A Report from the Drug-Resistant* Streptococcus Pneumoniae *Therapeutic Working Group* 18 THE PEDIATRIC INFECTIOUS DISEASE JOURNAL 1 at 5 (January 1999) ("Higher doses of clavulanate would be expected to lead to a greater incidence of diarrhea.") (attached).

Unit dosing, for Augmentin® or Augmentin ES-600™, very clearly would require extensive labeling changes and careful clinical study. For example, the labeling could be re-written to instruct patients to reconstitute each "unit dose" tablet but follow the approved dosing schedule. This would likely require labeling that instructs caregivers to discard unused amounts of the "swirl" each time they dose the drug. Contrary to the proposed labeling, clear warnings would be needed instructing patients ***not*** to drink the entire amount. At a minimum, actual usage and labeling comprehension studies would be needed before the safety and effectiveness of the products could be assured. *See* 21 CFR 312.3(b), 314.108(a) (describing clinical studies as including any experiments in which a drug is administered or dispensed to human subjects); *see also* FDA Docket No. 01P-0302/CP1, Letter from G. Buehler (April 12, 2002) (denying a suitability petition in part on the need for clinical studies in an actual use setting).

Alternatively, the petitioner may be seeking to eliminate the approved dosing schedule and, instead, dose each reference product only in unit dose increments. That, however, would be contrary to the approved labeling and, again, would require clinical study. A "flatter" dosing schedule for these products cannot be implemented through the mere filing of a suitability petition; clinical study is needed, for example, to determine whether pediatric patients less than 16 kg can tolerate a 600 mg amoxicillin starting dose and whether other intermediate doses can be eliminated. *See* 21 CFR 314.93(e) (requiring the denial of a suitability petition if investigations must be conducted to show the safety and effectiveness of the proposed product); *see also* FDA Docket Nos. 01P-0130/CP2 & 01P-0283/CP1, Letters from G. Buehler (July 9 & 3, 2002) (denying suitability petitions and stating that "a change in dosing regimen is not petitionable under Section 505(j)(2)(C) of the Act").

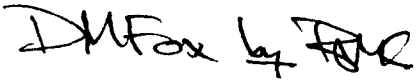
IV. CONCLUSION

Far from seeking solely a change in dosage form, the Petition effectively seeks to move patients to "unit dosing." For pediatric products such as Augmentin® and Augmentin ES-600™, this change is fundamental. Either the petitioner must develop new labeling to instruct patients on how to use the tablets to match the approved dosing schedule, or the petitioner must develop an entirely new dosing schedule to fit its dosage form. Either approach would require extensive changes to the approved labeling and raise significant questions of safety and

effectiveness. Finally, the Petition seeks a declaration with regard to a dosage form that FDA has yet to recognize and for which there are no established standards.

For each of these reasons, the Petition must be denied. As always, we thank you for your time and careful attention to these matters.

Sincerely,



David M. Fox

Attachment

cc: Gary Buehler, Director, Office of Generic Drugs
Martin Shimer, Project Manager, Office of Generic Drugs