

May 26, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Docket No. 2004P-0131
Comments to ANDA Suitability Petition for TOFIN™
(tobramycin solution for inhalation)

Dear Sir or Madam:

Drug Royalty Corporation Inc. (DRC) submits these comments in opposition to the suitability petition submitted by SourceCF requesting permission to file an abbreviated new drug application (ANDA) for a generic version of Chiron Corporation's (Chiron's) approved TOBI® (tobramycin solution for inhalation). For its product TOFIN™ (tobramycin solution for inhalation), SourceCF proposes to make several significant changes to the reference listed drug, TOBI, including different formulation concentration and product volume, and administration with a different delivery device.

The changes proposed by SourceCF, however, are similar to changes that the Food and Drug Administration (FDA) has considered and rejected for other inhaled drug products.^{1/} And, FDA's past comments about inhaled drugs lead to the conclusion that these changes could affect the drug's safety and effectiveness and that clinical studies are necessary before the product can be approved. For these reasons, FDA should deny SourceCF's petition.

I. Abbreviated New Drug Applications (ANDAs)

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch Waxman Amendments), a generic drug manufacturer can seek approval of a generic drug without showing safety and effectiveness if the generic

^{1/} See FDA Response to SensorMedics Corporation Suitability Petition, Docket No. 02P-0448/CP1 (Dec. 17, 2003) (denying a suitability petition requesting, among other things, a change in total drug content and use of a different device to administer albuterol inhalation solution).

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version is the “same as” an approved drug. *See* 21 USC 355(j). The ANDA will be approved if the generic version has the same active ingredient(s), dosage form, strength, route of administration, bioavailability, and labeling as the approved drug. 21 USC 355(j).

If, however, the proposed generic has a different active ingredient, dosage form, strength, or route of administration, the generic manufacturer must first request and receive approval of those changes in a suitability petition before an ANDA can be submitted. *See* 21 USC 355(j)(2)(C); 21 CFR 314.93. Although limited confirmatory tests may be submitted to show that the proposed changes do not affect safety and effectiveness, “FDA does not intend to permit petitioners to substitute limited confirmatory testing for clinical studies or otherwise [to] circumvent NDA requirements.”^{2/} Therefore, suitability petitions shall not be approved where the agency determines that clinical studies are needed to demonstrate the safety and effectiveness of the generic drug. *See* 21 USC 355(j)(2)(C); 21 CFR 314.93.

II. Clinical Studies On TOFIN Are Required

DRC concurs with Chiron’s April 20, 2004 comments that SourceCF’s suitability petition should be denied because additional clinical studies are needed to demonstrate the safety and effectiveness of TOFIN.^{3/} SourceCF proposes significant changes from the reference listed drug – increased formulation concentration (60 mg/ml to 100 mg/ml) in a smaller volume (5 ml to 1.9 ml), decreased administration time (15 minutes to 3 minutes), and use of a different delivery device.

FDA has long taken the position that the formulation composition and design of the drug delivery system of inhalation products raise concerns about consistent drug quality and performance.^{4/} Because inhalation products are

^{2/} 57 FR 17950, 17957-58 (Apr. 28, 1992); *see also* 54 FR 28872, 28880 (July 10, 1989). Limited confirmatory tests are “simple studies intended to rule out unlikely problems” and do not include animal or clinical studies that are required to demonstrate a drug’s safety or effectiveness. 57 FR at 17958.

^{3/} *See* Chiron Comments on ANDA Suitability Petition for TOFIN, at 1, 2-3 (Apr. 20, 2004) (the Chiron Comments).

^{4/} *See, e.g.,* Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (July 2002) (the Inhalation Guidance); Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing, and Controls Documentation (Oct. 1998); FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding

intended for direct delivery to the respiratory tract, small changes in the formulation or delivery system can affect the product's safety and effectiveness.^{5/} For instance, the design of the delivery device can affect particle/droplet size distribution, which FDA considers a "critical parameter" and "crucial for maintaining the quality of both solution and suspension formulated inhalation spray drug products."^{6/} In fact, FDA stated that "[f]rom a pharmaceutical viewpoint, the aerodynamic particle/droplet size distribution of the outgoing spray is one of the most important parameters for an inhalation product." *Id.* In the context of metered dose inhalers (MDIs), FDA has noted that increased particle size distribution could result in increased side effects due to greater absorption in the lungs, whereas decreased particle size distribution may lead to less effectiveness at the site of action.^{7/}

Given these potential outcomes, when changes to an inhalation spray product could affect particle/droplet size distribution, FDA recommends that these changes "be carefully evaluated for their effect on the safety, clinical effectiveness and stability of the product."^{8/} Moreover, FDA has made clear that delivered respirable dose – the primary criterion SourceCF relies upon in its petition – is not always an adequate measure of particle/droplet size distribution.^{9/} These factors combine to raise serious concerns about the safety and effectiveness of SourceCF's proposed product.

III. ANDA Approval Is Not Available For TOFIN

DRC also agrees with Chiron that the appropriate vehicle for obtaining approval of TOFIN is through the submission and agency approval of an NDA, not an ANDA. *See Chiron Comments* at 4-6. SourceCF's proposed changes to TOBI's

Because of Reasons of Safety or Effectiveness (Docket No. 00N-1357) (June 27, 2000) (the Concept Paper); Interim Guidance for Documentation of *In Vivo* Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers) (Jan. 27, 1994); Transcript of the April 26, 2000 Meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science.

^{5/} *See, e.g.*, Concept Paper at 29-30.

^{6/} Inhalation Guidance at 20.

^{7/} Concept Paper at 30.

^{8/} Inhalation Guidance at 4 (emphasis added).

^{9/} *Id.* at 21. The reproducibility of dose and geometry of the spray plume are also important factors, and like particle size distribution, they too can be affected by device design. *Id.* at 20, 22.

formulation concentration, volume, administration time, and delivery device are so significant that the pre-market review of TOFIN, a drug/device combination product, falls outside of the Office of Generic Drug's (OGD's) purview.

FDA has stated, with respect to MDIs, that OGD review is limited to products that are "essentially the same" as the innovator product – *i.e.*, "same formulation, same device" products.^{10/} In other words, the proposed generic and innovator products and their delivery device systems should be "functionally equivalent."^{11/} On the other hand, when a manufacturer proposes "significantly different" changes to the innovator product, the product cannot be marketed until an Office of New Drug (OND) review division determines that the proposed drug is safe and effective.^{12/} For instance, FDA implied that a proposed albuterol MDI product with a different spray pattern resulting from the use of the same MDI canister but different actuator would be reviewed by an OND division, not the OGD.^{13/} Therefore, for products with a "new formulation, new device" or "same formulation, different device," the agency recommends clinical studies to demonstrate safety and effectiveness of the proposed changes. *Id.* at 5-6. These principles are equally applicable to TOFIN because the scope of the proposed changes (including the drug delivery system) raises similar safety and effectiveness concerns.

It is clear from a quick review of the SourceCF petition that TOFIN is not the "functional equivalent" of TOBI. TOFIN makes four significant changes to the reference product – taking it far from "functional equivalency" in either drug formulation or delivery mechanism. Thus, the principles FDA has established to govern generic approvals of inhaled products compel the conclusion that SourceCF's suitability petition must be denied.

^{10/} See FDA Response to Glaxo, Inc. Citizen Petition, Docket No. 94P-0139, at 6 (Feb. 1996) (denying Glaxo's request to withdraw the Interim Guidance for Documentation of *In Vivo* Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)) (Jan. 27, 1994) (the Glaxo Letter); see also FDA Response to Schering-Plough Research Institute Citizen Petition, Docket No. 95P-0056 (Feb. 8, 1996).

^{11/} Glaxo Letter at 5.

^{12/} *Id.* at 6.

^{13/} *Id.* at 5 (the agency stated that such a "categorically different" product would not be covered by an interim guidance intended for ANDA applicants of generic albuterol MDI products).

IV. Conclusion

The collective effect of changes in the formulation concentration, volume, administration time, and delivery device that SourceCF proposes could affect the safety and effectiveness of TOFIN. FDA must evaluate the proposed particle/droplet size distribution of TOFIN's formulation in connection with the different device to assure a safe and effective product – something it cannot do under an ANDA. Therefore, DRC respectfully requests that the agency deny the suitability petition.

Sincerely,


Behzad Khosrowshahi
President and Chief Executive Officer
Drug Royalty Corporation Inc.

cc: Meredith Manning, Esq.
Hogan & Hartson, LLP