



October 8, 2004

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

Re: Docket No. 2004P-0131 (Dated March 11, 2004)  
Comments to ANDA Suitability Petition for  
TOFIN™ (tobramycin solution for inhalation)

Dear Sir or Madam:

Corus Pharma, Inc. is submitting Comments in response to the SourceCF petition requesting permission to file an Abbreviated New Drug Application (ANDA) for TOFIN™ (tobramycin solution for inhalation). The petition portrays the new product (TOFIN) as “clearly comparable” to the reference product (TOBI®, tobramycin solution for inhalation). However, TOFIN is not comparable to TOBI because TOFIN uses a different drug concentration, different solution volume, different drug dose, and different delivery device. The uncertainty of these combinations necessitates both clinical and nonclinical studies to support safety and efficacy of TOFIN.

Although Corus did not develop TOBI, many of the employees at Corus were directly involved in the TOBI development program and understand its intricacies.

Corus Pharma agrees with earlier comments submitted to the Division of Dockets Management (Chiron Corporation, dated 20 April 2004; and DrugRoyalty, dated May 26, 2004) detailing the reasons the petition does not meet the requirements for approval.

In this Comments letter, Corus will provide published evidence to show that a safe and effective outcome cannot be predicted by changing drug product parameters, drug dose, and delivery device without adequate studies.

**Point 1:** Drug delivery devices are substantially different between TOBI and TOFIN. The FDA has recognized that results between different delivery devices are not comparable, even when using the same drug product. In the Safety Review of the Summary Basis of Approval (SBA) for TOBI (NDA 50,753), the medical officer chose not to use the safety results from a Phase 2 study because a modification occurred in the nebulizer used for the Phase 3 studies compared to the Phase 2 study. The dose was the same. The medical officer stated that “while the results of [Phase 2] are encouraging regarding the tolerability of TOBI and the relatively low mean serum concentrations, a different nebulizer (the modified Pari LC) was

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utilized in the Phase III trials (PC-TNDS-002 and PC-TNDS-003). Therefore, [Phase 2] data regarding pharmacokinetics, safety, and tolerability are not relevant to the Phase III trials and to the nebulizer system ..." (SBA, Page 2, Safety Review of NDA, NDA 50,753).

The device proposed for delivering TOFIN (Pari eFlow®, vibrating piezoelectric membrane) is substantially different than the delivery device for TOBI (Pari LC Plus®, jet nebulizer). When comparing the drug delivery systems between TOBI and that proposed for TOFIN, substantially greater differences are apparent than the differences between the Phase 2 and Phase 3 studies of TOBI.

**Point 2:** An untested device may not function as expected unless it has been studied in the manner in which it is to be used. In Geller et al (Chest **123**: 28-36; 2003), 10 of 53 patients had device problems with the test device. Their device used a piezoelectric mechanism to generate aerosol, the same mechanism used in the eFlow from Pari in the TOFIN petition. Failure can be caused by human factors, mechanical issues, or the drug solution, and needs testing.

**Point 3:** Drug formulation and dose are substantially different between TOBI and TOFIN. The proposed drug product for TOFIN (95 mg/mL) is more concentrated than TOBI (60 mg/mL), yet the nominal dose to be delivered for TOFIN (190 mg tobramycin) is less than TOBI (300 mg). Weber et al (Pediatr Pulmonol **23**:249-260;1997) have shown that the physical properties of antibiotic formulations including antibiotic concentration have an effect on nebulization rates and particle size. Changes in these parameters may cause irritation to the respiratory mucosa.

**Point 4:** An untested drug product coupled with an untested device is unpredictable. TOFIN and the Pari eFlow need long-term testing to demonstrate safety and effectiveness. Tinnitus is an adverse event that is sentinel to hearing loss. In the TOBI NDA, it was noted that tinnitus occurred significantly higher in patients on TOBI versus placebo. Does the untested combination of TOFIN and the eFlow effect tinnitus? Does the combination effect tinnitus in children? Are there adverse events unique to the proposed combination?

In conclusion, Geller et al (Chest **123**: 28-36; 2003) demonstrated that effective combinations potentially exist between drug product and delivery device. However, the authors concluded that clinical testing should be performed to support further device development and ensure effective treatment for CF patients. Corus Pharma agrees with this prudent approach.

Sincerely,

Handwritten signature of A. Bruce Montgomery in black ink.

A. Bruce Montgomery, M.D.  
CEO