



Excerpt of footnote 1 from Letter from Andrx Pharmaceuticals, Inc. to FDA  
(dated October 5, 2001), released under the Freedom of Information Act  
(redactions appeared in original)

Andrx believes the 240 mg product failure arose from the company's efforts to optimize the manufacturing process, within the specifications set forth in ANDA No. 75-401. Andrx provided Biovail samples from five different Taztia batches produced in January 2001 (one of each product strength, including 50 capsules from Lot #698B001 (240 mg)). The ANDA specifies a drying time for coated extended-release pellets of not less than \_\_\_\_\_ hours. The pellets in the batch used for Andrx's 360 mg biostudies were dried for \_\_\_\_\_ hours. The batches provided to Biovail, by contrast, were dried for \_\_\_\_\_ hours. Both of these drying times met the specification of ANDA No. 75-401.

Andrx learned in May 2001 that Lot #696B001 (the 240 mg product provided to Biovail) failed long-term stability at the 3-month station, due to a high dissolution rate at the 4-hour time point. The upper limit of the ANDA specification is \_\_\_\_\_ at four hours; the lot in question showed a mean value of 44%. All other lots, including the 120 mg Taztia product provided to, and tested by, Biovail (Lot #696B001), remained within specification after 3 months. Indeed, Biovail may have selected this lot based on the high dissolution result that would have been observed at that time.

Subsequent work at Andrx revealed that the dissolution failure in the scale-up batches arose from the use of a shorter drying time relative to the ANDA batches, and that failures arise within two to three weeks following encapsulation. As part of its process validation work, Andrx has learned that Taztia is extremely sensitive to even small changes in the extended-release coating step, such as drying time, spray rate, and atomization pressure.

Andrx ultimately reverted to processing parameters that are identical to the parameters used for production of Andrx's biobatches submitted in ANDA No. 75-401, with one exception (i.e., the spray rate for part C in the optimized process is \_\_\_\_\_ used in the biobatches). All processing parameters specified in Andrx's current validation study are fully optimized, based on experimental data that includes room temperature stability results. All of the processing parameters are within the parameters of the batch record submitted to ANDA No. 75-401, and closely conform to the parameters used for production of the original ANDA biobatches. The most critical of the parameters has been shown to be the drying time, and the current process adheres to the \_\_\_\_\_-hour drying time that was used for the ANDA biobatches. On-going stability studies on the original ANDA biobatches have shown that product manufactured with Andrx's optimized process is stable at the 30-month time point. In light of its experience, Andrx intended to revise its ANDA batch record to tighten the drying time specification, as well as the spray rate and atomization pressure parameters, and report these changes in the first post-approval annual report. These changes fall within the definition of SUPAC-MR Level 1 Manufacturing Process Changes (i.e., "process changes involving adjustment of equipment operating conditions ... within original application ranges").