

T A B B

DECLARATION OF ROBIN MORRISON

1. I, Robin Morrison, am employed by GlaxoSmithKline ("GSK") as Sourcing Manager, Worldwide Technical Procurement, for Inhaled Products, within GSK's Global Manufacturing & Supply organization. I have held this position since approximately October 2000. I am based at GSK's manufacturing facility in Barnard Castle, England, which is the lead manufacturing site for Flonase® (fluticasone propionate) Nasal Spray ("Flonase"). I have a BSc Honours degree in Applied Science (Robert Gordons University- Aberdeen, UK) and was trained in statistics as part of my degree.

2. As a technical sourcing manager, I am responsible for securing adequate supplies of manufacturing components that meet all applicable regulatory and other quality standards. This entails working with current and prospective suppliers to evaluate the fit between their capabilities and GSK's needs, and further – if a supply relationship is to be established or maintained – making sure that GSK's needs are effectively met. Because Flonase is within my area of responsibility, I interact extensively with GSK's external suppliers for nasal spray product components (such as pumps and actuators), as well as with GSK managers and technical experts who have manufacturing and quality control responsibilities for the product.

3. In 1999, at the behest of the United States Food and Drug Administration ("FDA"), GSK began working on a supplemental application that would, among other things, implement revised and new product specifications, including acceptance criteria for certain release tests done on the product. Among the new specifications being discussed were droplet size distribution ("DSD"), and spray pattern ("SP"), which are

ways of assessing the performance and quality of an intranasal product (specifically, the characteristics and consistency of the spray it emits).

4. Developing DSD and SP acceptance criteria to FDA's satisfaction was technically challenging, and ultimately required GSK to take part and invest in an extensive research and development collaboration with the supplier of pumps and actuators used in Flonase. (Hereafter I will refer to this research and development collaboration as the "Project"). Technical experts from GSK and its supplier worked in close collaboration to design and conduct a series of experiments to identify sources of variability in product performance, and to engineer improvements to key elements that were ultimately identified as the leading sources of variability. The Project team, with representatives from both firms, met frequently over a period of years and communicated extensively with FDA (including two face-to face meetings with agency personnel) for the purposes of seeking guidance, reporting progress, and confirming the acceptability of the approach being taken. The net result was the replacement of actuators formerly used in Flonase with *modified* actuators made with new or modified equipment (specifically, one new actuator mold, five modified actuator molds, and four modified assembly tools), to meet the objective of achieving even greater consistency of Flonase's performance in DSD and SP testing.

5. I have been directly and personally involved in the Project since its inception. The first stage of the Project was a diagnostic exercise that began in early 2001 and continued through April 2003. During this stage, GSK and its supplier collaborated to identify the leading sources of variability in the performance of Flonase in DSD and SP testing. The approach was first to draw on the collective knowledge within

both firms to identify the variables (those elements of the spray delivery system, as well as of the analytical methods for conducting DSD and SP tests, that might, if adjusted or more precisely controlled, contribute to a reduction in variability), and then to design and conduct a series of experiments to systematically evaluate the relative significance of each of the identified variables.

6. The second stage of the Project was a trial that ran from April 2003 to October 2003. During this stage, changes were made (but not yet implemented in commercial production) to those elements that had been identified as relatively significant potential contributors to a reduction in variability, and the impact of those changes was measured. In June 2003, representatives of both GSK and its supplier met face-to-face with FDA. The purpose of this meeting was to report on the work that had been done and to confirm the agency's general acceptance of the approach being taken, in light of the measured positive effects of the changes.

7. The third stage of the Project involved implementation of the improvements to Flonase components and the process for manufacturing them. This stage lasted from October 2003 to April 2004, and also included a meeting with representatives of the FDA, in December 2003. The purpose of this meeting was to communicate the level of improvement observed and to gain agreement on interim standards necessary for the continued supply of Flonase to the marketplace, as the modified actuators and equipment to manufacture them were being implemented.

8. GSK made a final submission to FDA in April 2004, presenting a large body of data that had been generated from testing the modified components, and proposing new acceptance criteria for DSD and SP specifications reflecting these

extensive test results. Indeed, specifications for DSD were based on test results from a sample of 915 bottles. Acceptance criteria (the range of lowest to highest acceptable values) for the three parameters measured in DSD testing (three different percentile droplet size diameters) were established on the basis of a data set generated by actuating each of the 915 bottles 3 times, equating to 183 sub-lots of product (in actual lot release testing, the sample we test consists of five bottles, each of which is actuated three times; 183 multiplied by 5 equals 915). Specifications for SP were based on test results from a sample of 320 bottles. Acceptance criteria for X axis measurements and X/Y ratios were established on the basis of a data set generated by actuating each of the 320 bottles two times, equating to 160 sub-lots of product (in actual lot release testing, the sample we test consists of two bottles, each of which is actuated two times; 160 multiplied by 2 equals 320).

9. On October 15, 2004, FDA approved the proposed acceptance criteria, culminating years of challenging work.

10. The Project resulted in improvements in the consistency of the DSD and SP data for Flonase, as reflected by tight acceptance criteria for the two tests. One common gauge of consistency (variability) in product performance is relative standard deviation ("RSD"). The RSD of any data set (for instance, the data sets underlying the newly approved acceptance criteria for DSD and SP testing of Flonase) is calculated by expressing the standard deviation of the data as a percentage of the mean (average) value of the data. (Standard deviation is itself a measure of the range (breadth) of data points in a set.) Broadly speaking, the greater the RSD, the greater the variability of the parameter being measured. As a result of the Project, variability in the Flonase® (NSI) data had

decreased, for the three parameters (droplet size diameter percentiles) that are measured, from 1999 proposed levels of approximately 9% RSD for all three parameters, to post-Project levels of 6.6%, 7.9%, and 8.0%, respectively. These reflect 30%, 15%, and 9% *reductions* in the %RSDs. Likewise, the variability in the SP data had decreased from 14.7% and 9.2% RSD for the two parameters that are measured (X axis and the ratio of X and Y axes), to 11.3% and 6.5% RSD, respectively. These reflect 23% and 29% reductions in the %RSDs.

11. GSK and its parts supplier have devoted substantial financial and human resources to the Project. For most of the first two stages, which collectively lasted for more than two years, GSK assigned three full-time equivalents to support the Project. Overall, significant effort has been expended in modifying Flonase components to FDA's satisfaction, with the goal of continued enhancements to product quality.

I declare, under penalty of perjury, that the foregoing is true and correct.

Executed on:

22-D NOVEMBER 2004
Date

Robin Morrison
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