



GlaxoSmithKline

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### CITIZEN PETITION

On behalf of GlaxoSmithKline ("GSK"), the undersigned submit this citizen petition under sections 501 and 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 CFR § 10.30, among other provisions of law, to ensure that proposed generic fluticasone propionate nasal spray products meet the same high standards of quality as GSK's brand-name product, FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg.

On October 15, 2004, the Food and Drug Administration ("FDA") approved supplement S-019 to GSK's new drug application ("NDA") 20-121 for FLONASE. This supplement represented the completion of a Phase IV commitment that GSK had undertaken at FDA's behest, and was the culmination of more than four years of collaborative effort involving FDA, GSK, and GSK's component supplier. S-019 provided for tightened specifications for droplet size distribution ("DSD") and spray pattern ("SP") for FLONASE, reflecting distinctly lower inter- and intra-batch variability than had previously characterized the product.

It is fundamental that all drug products must be manufactured and tested in a manner that ensures their identity, strength, quality, and purity. *See* 21 USC §§ 351, 355(d)(3), 355(j)(4)(A). It is likewise fundamental that FDA must apply its standards in an even-handed manner to similarly situated persons and products. *See* 5 USC § 706(2)(A); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) ("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the [Administrative Procedure Act].") (quotation removed). In requiring GSK to adopt tight DSD and SP specifications for FLONASE, FDA set a rigorous standard of quality that must now be applied to similarly situated fluticasone propionate nasal spray products. To do otherwise

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particularly for generic products that purport to be the same as FLONASE – would be arbitrary, capricious, and contrary to law.<sup>1</sup>

## I. ACTION REQUESTED

The undersigned hereby request that the Commissioner of Food and Drugs (the “Commissioner”) refrain from approving any abbreviated new drug application (“ANDA”) for a fluticasone propionate nasal spray product unless the product is shown to meet the same standards of product quality as FLONASE, as recently approved under S-019. In particular, any such ANDA must include comparably rigorous specifications for DSD and SP, and must be shown to meet comparable standards of consistency (*i.e.*, low variability) for these key measures of quality.

## II. STATEMENT OF GROUNDS

### A. Statutory and Regulatory Background

The standards of quality that the FDCA imposes on drug products subject to FDA approval are uniform, regardless of whether the application for approval takes the form of an NDA or an ANDA.

In evaluating an application for approval, the quality standards that FDA must apply are the same for NDAs and ANDAs. The agency must refuse to approve an NDA if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, *quality*, and purity . . .” 21 USC § 355(d)(3) (emphasis added); *see* 21 CFR § 314.125(b)(1). Similarly, an ANDA must not be approved if “the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, *quality*, and purity . . .” 21 USC § 355(j)(4)(A) (emphasis added); *see* 21 CFR § 314.127(a)(1).

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<sup>1</sup> On October 25, 2004, GSK submitted a letter to FDA’s Office of Generic Drugs (“OGD”), informing OGD of the approval of S-019 and encouraging OGD to consult with the Division of Pulmonary and Allergy Drug Products regarding the quality standards that had been applied to FLONASE. GSK also has formally petitioned FDA to issue a final and complete guidance document on bioavailability and bioequivalence testing for nasal spray products, before acting on any generic applications for fluticasone propionate products. *See* GSK Citizen Petition, Docket No. 2004-0239 (May 19, 2004); *see also* Docket Nos. 2004P-0348 & 2004P-0206.

Consistent with the identical statutory approval standards, the chemistry, manufacturing, and controls (“CMC”) information that must be submitted as part of NDAs and ANDAs is likewise identical. The CMC section of an NDA must contain, *inter alia*:

[A] statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; . . . a description of the manufacturing and packaging procedures and in-process controls for the drug product; [and] such specifications and analytical methods as are necessary to assure the . . . quality . . . of the drug product.

21 CFR § 314.50(d)(1)(ii)(a). With one exception not relevant here, the CMC section of an ANDA must contain the identical information. *See id.* at 21 CFR § 314.94(a)(9).

FDA’s criteria for making “therapeutic equivalence” determinations reinforce the uniformity of quality standards. For two products to be considered therapeutically equivalent and therefore substitutable for one another, they must be both “pharmaceutically equivalent” and bioequivalent. To be pharmaceutically equivalent, brand-name and generic drugs must be in the identical dosage form, and must:

[C]ontain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety . . .; [need] not necessarily contain the same inactive ingredients; and [must] *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*

*Id.* at § 320.1(c) (emphasis added); *see* Approved Drug Products with Therapeutic Equivalence Evaluations (2004) (the “*Orange Book*”) at Preface 1.2. The agency thus requires any product that purports to be “the same as” a brand-name drug to meet the identical standard of quality as that drug.

Finally, the statutory provisions that regulate product quality on an ongoing basis, under the rubric of “adulteration,” are the same. Under the FDCA, a drug product (such as FLONASE) that is not recognized in an official compendium is adulterated if, among other things, “its strength differs from, or its purity or *quality* falls below, that which it purports or is represented to possess.” 21 USC § 351(c) (emphasis added). This standard applies equally to all drug products, regardless of their route to approval. *See* 21 CFR § 314.170 (“All drugs . . . are

subject to the adulteration and misbranding provisions in sections 501, 502, and 503 . . .”). Thus, a generic product that purports to be “the same as” FLONASE must meet the same standard of quality as FLONASE.

## **B. Scientific Background**

### **1. *The Importance of In Vitro Controls***

A uniform standard of product quality, including adequate manufacturing controls, is particularly important for nasal spray products, as the performance of any product is critically dependent on the performance of its constituent device components. The extent to which the active ingredient in a nasal spray product reaches the site of action depends not on systemic absorption, but rather upon topical delivery of liquid droplets or particles to nasal mucosa. See Draft Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003) (“Draft BA/BE Guidance”) at 4.

This means that the “spray producing” components of nasal spray products (e.g., the pump, actuator, and actuator orifice) are critical for ensuring the reproducible delivery of the drug formulation. See Guidance for Industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (July 2002) (“CMC Guidance”) at 2-3. The importance of consistent DSD and SP, in particular, to the quality and performance of such products is well documented. As the CMC Guidance states:

The particle/droplet size distribution is a critical parameter, and its control is crucial for maintaining the quality of both solution and suspension formulated inhalation spray drug products. This parameter is dependent on both the formulation and the container closure system.

*Id.* at 24; see also Draft BA/BE Guidance at 5 (“From a product quality perspective, the critical issues are release of drug substance from drug product and delivery to the mucosa.”). The device components of nasal spray products that contribute to the formation of droplet size and spray pattern, including the actuator, are therefore expected to be “as close as possible in all critical dimensions” to those of the reference product. Draft BA/BE Guidance at 7. The metering chamber volume, actuator orifice diameter, and nominal spray angle of the actuator insert are all expected to be the same, as between test and reference products. See *id.*

## 2. *The Measurement of DSD and SP*

Because droplet size is “an important property influencing the nasal deposition of aerosols and sprays,” the agency recommends that it be thoroughly characterized using laser diffraction or a similar validated methodology. *Id.* at 13. Laser diffraction is an optical tool for measuring the geometric size of all individual droplets in flight during the course of an entire spray. *See id.*

Measures of droplet size distribution, as determined by laser diffraction, are typically expressed in terms of mean percentile diameter sizes. In these measurements, D“X” represents the diameter size at the Xth percentile D, such that X% of a spray’s droplets have been measured to be smaller than D, and 100 – X% have been measured to be larger than D. A D10 of 30  $\mu\text{m}$ , for example, would indicate that 10% of the measured droplets in a spray are smaller than 30  $\mu\text{m}$ , while 90% are larger than 30  $\mu\text{m}$ . A “Mean” D10 of 30  $\mu\text{m}$  would indicate that, after some number of units of a batch have been tested, the average D10 of all of the sprays was 30  $\mu\text{m}$ . GSK’s specifications for DSD testing establish “acceptance criteria” (*i.e.*, ranges for lowest to highest acceptable values) for three different mean percentile diameter measures.

Droplet size distribution specifications play an important role in regulating the quality of nasal spray products. Consistent performance in DSD testing helps to ensure the quality of the product as it is manufactured and released. *See generally* CMC Guidance at 15.

Likewise, spray pattern is a significant indicator of the performance of a nasal spray product. The pump and the actuator, and the size and shape of the spray orifice, among other things, can influence SP. *See id.* at 14. SP testing assesses the two-dimensional (cross-sectional) shape of the spray emitted by a product. Typically, SP testing is conducted through impaction techniques. Such techniques involve taking a “picture” of the spray pattern by spraying the product onto a suitable collection surface from a set distance and developing the image. *See* Draft BA/BE Guidance at 17-20. GSK’s specifications for SP establish acceptance criteria for both the length of the X axis (*i.e.*, the longest diameter of the spray pattern, expressed within a range, such as  $\geq$  “P” cm and  $\leq$  “Q” cm), and for the X/Y or “ovality” ratio (*i.e.*, the ratio between the longest and shortest axes of the pattern, expressed as a single limit, such as  $\leq$  “N”).

DSD and SP specifications thus represent key standards that are important to confirming the quality of the drug product. *See* CMC Guidance at 44 (defining “Specification”).

### 3. *Indicators of Variability*

Two common indicators of the variability of a product's *in vitro* performance are standard deviation ("SD") and percent relative standard deviation ("% RSD"). The SD of any data set (such as DSD or SP testing results) is a measure of the variation, or spread, of the individual data points in that set. The % RSD is a measure of the SD of the data expressed as a percentage of its mean. It is calculated by dividing the SD of the data by its mean, and multiplying by 100. This provides an estimate of how much, on average, each individual data point differs from the mean of the entire set.

For example, a product with a spray pattern that is consistent lot-to-lot would produce data exhibiting a relatively low SD and % RSD, because each individual measurement would be relatively close to the mean of all of the data. A product with a pattern that is inconsistent lot-to-lot, on the other hand, would produce data exhibiting a larger SD and % RSD. The agency relies on statistical indicators, including % RSD, to evaluate the degree of product quality and specifications established to control for it. *See, e.g., infra* at section II.C.

SD and % RSD thus are important absolute indicators of the quality of data for an *in vitro* test parameter. Low variability for an *in vitro* test is an indication of high product quality. It is also an indication of the precision of the analytical test method and measurement system used to collect the data.

Moreover, it is important to differentiate between *in vitro* tests of product quality versus comparative *in vitro* studies used to establish bioequivalence. The parameters discussed above (DSD and SP), when analyzed using SD and % RSD, characterize the absolute quality of the product. In contrast, *in vitro* bioequivalence studies establish the relative performance of a test and reference product (typically, a proposed generic product compared with an innovator product). As the agency has recognized:

Generally, [product quality] tests help characterize the identity, strength, quality, purity, and potency of the drug product and assist in setting specifications (tests, methods, acceptance criteria) to allow batch release. These tests have a different purpose than do BA/BE tests . . . .

Draft BA/BE Guidance at 6. This is so, even where a product quality test and a BE test measure the same parameters (*e.g.*, DSD and SP), because the analysis applied to each is different. *See id.* Thus, separate and apart from BE testing, product

quality must be evaluated on an absolute basis, to assess whether applicable quality standards are being met with acceptably low variation.

### **C. Factual Background**

#### **1. FLONASE Nasal Spray**

First approved on October 19, 1994, FLONASE is a corticosteroid nasal spray used to treat the nasal symptoms of seasonal and year-around allergies, as well as nonallergic rhinitis. The product consists of an aqueous suspension of microfine fluticasone propionate intended for topical administration to the nasal mucosa through a specifically engineered metering atomizing pump. See FLONASE Labeling at 1 (attached at Tab A).

FLONASE is supplied in an amber glass bottle fitted with the metering atomizing pump, a white nasal adaptor, and a green dust cover. Inside the nasal adaptor, an actuator directs the suspension from the pump through an insert and into a swirl chamber, where it is then released through a spray orifice for delivery into the nostril.

FLONASE is thus a drug/device combination product, in which the quality and performance of the spray device is critical to the safety and effectiveness of the approved product. As discussed above, the maintenance of a certain droplet size distribution and spray pattern are indicators of accurate and consistent delivery of the active ingredient to the nasal site of action.

#### **2. The Phase IV Commitment**

Prior to 1997, GSK's nasal spray products had been approved without specifications for DSD or SP. In that year, however, FDA's Division of Pulmonary Drug Products (now the Division of Pulmonary and Allergy Drug Products) (the "Division") began to seek new controls (including DSD and SP) on GSK's products, beginning with Beconase AQ® (beclomethasone dipropionate monohydrate) Nasal Spray, 0.042% (NDA 19-389), and subsequently including FLONASE.

The agency has since been consistent in its emphasis on the importance of DSD and SP. In 1997, the Division's (then) Supervisory Chemist Guirag Poochikian, Ph.D.,<sup>2</sup> remarked that the agency considered DSD and SP to be

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<sup>2</sup> Dr. Poochikian has since been promoted to the position of Associate Director for Regulatory Science for the Office of New Drug Chemistry ("ONDC") within the Office of Pharmaceutical Science, Center for Drug Evaluation and Research ("CDER"). The charge of the ONDC is to bring "the responsibility for the chemistry, manufacturing and controls (CMC) review process of new

critical performance tests and had been holding internal discussions on the subject. See Supplemental NDA 20-121/S-012 (July 30, 1999) (Minutes of Dec. 12, 1997, Meeting) (on file with the Division).<sup>3</sup> Subsequently, the CMC Guidance and the Draft BA/BE Guidance (now in its second edition) firmly established FDA's position that DSD and SP were essential quality standards for nasal spray products. See *supra* at section II.B.

On July 30, 1999, GSK submitted supplement S-012 to its FLONASE NDA. This supplement provided for an additional manufacturing facility for FLONASE. GSK requested that the Division review this supplement on an expedited basis, because the alternative facility was needed to assure a continuing supply of FLONASE to meet ever increasing demand.

GSK's supplement also provided for new specifications for foreign particulate matter, particle size distribution, uniformity of dose, number of medicated sprays, DSD, and SP. These specifications were included in response to the Division's earlier request for new manufacturing controls on GSK's nasal spray products. See Supplemental NDA 20-121/S-012.

On November 1, 1999, the Division issued an Approvable Letter for S-012, stating that for the supplement to be approved, GSK would need to address certain "deficiencies." These included a need for GSK to tighten the limits for both DSD and SP, as well as to decrease the variability found in GSK's DSD data. Specifically, the Division instructed GSK to take the following steps (among others):

- Take action to reduce the variation in % RSD for DSD data, which FDA noted (with disapproval) had varied considerably from one set of DSD data to the next;
- Test every batch at release for DSD;

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drugs together under one organization." *What is ONDC?*, at [www.fda.gov/cder/ondc/default.htm](http://www.fda.gov/cder/ondc/default.htm). According to the agency, "*this assures quality and consistency in the CMC review of new drugs across CDER.*" *Id.* (emphasis added). It is intended to assure that CDER's senior management structure is able to "speak with one voice" with respect to product quality for all innovator and generic products. *Id.*

<sup>3</sup> Throughout this citizen petition, GSK refers to supplemental NDAs, FDA action letters, and other material on file with FDA. GSK does not, however, waive or relinquish any of its rights to the confidentiality of such information under the Freedom of Information Act, FDA regulations, and any other applicable provision of law. See, e.g., 5 USC § 552(b)(4); 21 CFR § 20.61.

- Propose tightened data-driven specifications for DSD after addressing the concern about % RSD;
- Test every batch at release for SP; and
- Provide additional data for SP testing of initial batches and submit data-driven specifications for X-axis and X/Y ratio.

See Approvable Letter to NDA 20-121/S-012 (Nov. 1, 1999) (on file with the Division).

In a follow up to this letter, GSK held a telephone conference with the Division on November 10, 1999. Agency officials stated that those deficiencies specific to the proposed alternative manufacturing facility could be addressed by GSK in a complete response, which could allow manufacturing at that facility to begin. They directed GSK to address each of the remaining deficiencies, however, including those regarding DSD and SP, through a Phase IV commitment. See Amendment to Supplemental NDA 20-121/S-012 (Dec. 8, 1999) (on file with the Division).

The agency subsequently approved S-012, as amended by GSK's December 8, 1999, complete response. In its Approval Letter, the Division reiterated GSK's Phase IV commitment regarding, among other things, DSD and SP. See Approval Letter to NDA 20-121/S-012 (Feb. 18, 2000) (on file with the Division).

### **3. *The Approvable Letter***

On October 16, 2000, GSK submitted supplement S-019 to fulfill its Phase IV commitment (stemming from previously approved S-012) to FDA. With regard to DSD, GSK reported that, to reduce the % RSD per the Division's request, it had revised its analytical methodology such that a more consistent portion of the FLONASE spray could be measured. With this revised method, GSK proposed tightened specifications to be included in its NDA. See Supplemental NDA 20-121/S-019 (Oct. 16, 2000) (on file with the Division).

The Division, however, subsequently issued another Approvable Letter, again citing deficiencies. See Approvable Letter to NDA 20-121/S-019 (Apr. 13, 2001) (on file with the Division). Specifically, GSK was instructed (among other things) to:

- Work closely with its pump supplier to decrease pump inter- and intra-batch variability and tighten the pump performance acceptance criteria;
- Tighten the DSD acceptance criteria significantly; and
- Tighten the SP acceptance criteria for the X distance and X/Y ratio significantly.

*See id.* Again, the Division held to its rigorous expectations of product quality for FLONASE.

#### 4. *The Not Approvable Letter*

In its complete response to the Division's April 13, 2001, Approvable Letter, GSK committed to work closely with its pump and actuator supplier to decrease inter- and intra-batch variability for the DSD and SP specifications. *See* Amendment to Supplemental NDA 20-121/S-019 (Dec. 11, 2001) (on file with the Division). Based on a review of more than 200 batches of product, GSK proposed to tighten the acceptance range for two of the three mean percentile diameter size measures for DSD testing by approximately 50% each, and to tighten the acceptance range for the third DSD measure by approximately 30%. Given the state of the technology available for the manufacture of the FLONASE actuator, however, and after a similar review, GSK was unable to propose tighter SP specifications. *See id.*

Once again, GSK had been unable to meet the Division's expectations regarding standards for product quality. This time, the Division issued GSK a Not Approvable letter, stating that "the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the [FDCA] and 21 CFR 314.125(b)." *See* Not Approvable Letter to NDA 20-121/S-019 (June 11, 2002) (on file with the Division).<sup>4</sup>

In its Not Approvable Letter, the Division stated that the data provided in GSK's supplement did not support its proposed specifications, and that GSK needed to further tighten its DSD acceptance criteria. The Division also

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<sup>4</sup> Presumably, the statutory basis for the Not Approvable action was section 505(d)(3) of the FDCA (requiring that FDA refuse approval if the "methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [the] drug are inadequate to preserve its identity, strength, quality, and purity . . .").

requested the individual SP data supporting GSK's statistical analysis, and reiterated that its SP acceptance criteria "remain[ed] unacceptable." *Id.*

GSK then requested a meeting with the Division to discuss these deficiencies, and to seek agreement on a plan to optimize the molding and assembly processes for the FLONASE actuator to reduce the DSD and SP variability. *See Meeting Request (Mar. 28, 2003) (on file with the Division).* At the meeting, GSK described the results of a comprehensive investigation into the sources of DSD and SP variability, conducted in response to FDA's directive that GSK work with its parts supplier to decrease variability. Together, GSK and its supplier proposed a variety of changes to the manufacturing processes and to the FLONASE product itself, to address the deficiencies identified by the Division. *See Meeting Package (May 21, 2003); Minutes of June 18, 2003, Meeting (on file with the Division); see generally Declaration of Robin Morrison, Sourcing Manager, Worldwide Technical Procurement, for Inhaled Products, GSK at ¶¶ 4-8 (attached at Tab B).*

On December 15, 2003, GSK and its supplier presented to the Division the final modifications made to the FLONASE actuator and manufacturing processes. GSK agreed to submit a new supplement to provide for interim DSD acceptance criteria, to allow GSK to continue marketing FLONASE, while transitioning to its modified product components. *See Amendment to Supplemental NDA 20-121/S-019 (Jan. 9, 2004) (Minutes of Dec. 15, 2003, Meeting) (on file with the Division); see also Supplemental NDA 20-121/S-031 (submitted Jan. 16, 2004) (on file with the Division); Approval Letter for NDA 21-121/031 (Jan. 23, 2004) (on file with the Division).*

### ***5. Final Approval of S-019***

On April 30, 2004, GSK submitted its complete response to the Not Approvable Letter for S-019. GSK described again the extensive research and development collaboration that it had undertaken with its component supplier, at the Division's direction, to improve the FLONASE actuator molding and assembly. *See Amendment to Supplemental NDA 20-121/S-019 (Apr. 30, 2004) (on file with the Division).*

In its complete response, GSK proposed final DSD specifications for FLONASE. These specifications were based on test results from a sample of 915 bottles. Acceptance criteria (the range of lowest to highest acceptable values) for the three mean percentile diameter measures were established on the basis of a data set generated by actuating each of the 915 bottles three times, equating to 183 sub-lots of product. (In actual lot release testing, five bottles are sampled in each lot.) *See Amendment to Supplemental NDA 20-121/S-019 (Apr. 30, 2004).*

Variability in the FLONASE DSD data had decreased, from approximately 9% RSD for the three mean percentile diameter size measures, to 6.6%, 7.9%, and 8.0%. These reflect approximately 30%, 15%, and 9% reductions in the % RSDs compared to the data originally presented in S-019. See Amendment to Supplemental NDA 20-121/S-019 (Sept. 24, 2004); Declaration of Robin Morrison at ¶¶ 8-10.

GSK also proposed tighter specifications for SP. These specifications 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, two bottles are sampled in each lot.) The variability in the SP data had decreased from 14.7% and 9.2% RSD for the X axis and X/Y ratio to 11.3% and 6.5% RSD, respectively. These reflect 23% and 29% reductions in the % RSDs compared to the data presented earlier in S-019. See Amendment to Supplemental NDA 20-121/S-019 (Apr. 30, 2004); Declaration of Robin Morrison at ¶¶ 8-10.

Finally, on October 15, 2004, after having issued two Approvable Letters and one Not Approvable Letter, with continuing attention to specifications for DSD and SP over the course of more than four years, the Division approved S-019. See Approval Letter to NDA 20-121/S-019 (on file with the Division). As a result of this approval, GSK's DSD and SP specifications are now memorialized in the FLONASE NDA.

### III. ARGUMENT

The October 15, 2004, approval of S-019 brought to a conclusion a painstaking, expensive, and technically challenging effort to ensure the quality of FLONASE. GSK undertook this effort at FDA's insistence. Even more, GSK was required over the course of several years to tighten – and then *retighten* – its specifications for DSD and SP. These specifications have now been approved under the NDA for FLONASE and supersede any prior specifications with respect to these two critical performance measures. Indeed, should any individual batch of FLONASE fail to meet these standards, it may not be released, as it could be deemed unapproved and adulterated within the meaning of the FDCA. See 21 USC §§ 321(a) and (d), 351(a) and (c), and 355(a).

#### A. All Fluticasone Propionate Nasal Spray Products Must Meet Like Standards of Quality

##### 1. FDA must treat similarly situated sponsors alike

“Government is at its most arbitrary when it treats similarly situated people differently.” *Etelson v. OPM*, 684 F.2d 918, 926 (D.C. Cir. 1982). This bedrock principle has been applied time and again to ensure that people who are subject to the same legal standards are, to the fullest extent possible, treated the same. *See, e.g., Airmark Corp. v. FAA*, 758 F.2d 685, 692 (D.C. Cir. 1985) (striking down agency decision where “different decisional criteria” were applied to “similarly situated carriers,” resulting in a lack of “[e]lementary even-handedness”); *NLRB v. Washington Star Co.*, 732 F.2d 974, 977 (D.C. Cir. 1984) (“The present sometimes-yes, sometimes-no, sometimes maybe policy . . . cannot, however, be squared with our obligation to preclude arbitrary and capricious management . . .”).

It is a principle that is readily applicable to the regulation of foods, drugs, and medical devices, particularly where sponsors are vying to compete in the same market. For example, in *United States v. Diapulse Corp. of America*, 748 F.2d 56 (2d Cir. 1984), the court struck down FDA’s disparate treatment of two similarly situated medical devices, where one sponsor (Diapulse) sought to modify its device to match one that had been approved by FDA for another sponsor (United Medical Equipment). The court enjoined FDA from refusing to approve Diapulse’s product, while allowing the other to remain on the market, emphasizing that “[d]eference to administrative discretion or expertise is not a license to a regulatory agency to treat like cases differently.” *Id.* at 62; *see United States v. Undetermined Quantities . . . “Exachol,”* 716 F. Supp. 787 (S.D.N.Y. 1989) (rejecting FDA’s refusal to apply its policy on health claims for food products evenly across similarly situated products).

The clearest expression of this principle – and the one that dictates the outcome of this petition – is found in *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997). There, plaintiffs alleged that FDA had decided to regulate some ultrasound contrast agents as medical devices and others as drugs, for no apparent reason. *See id.* at 24. That decision – in and of itself – may have passed muster, had FDA not been “apparently applying very different standards to assess the safety and effectiveness of essentially identical products.” *Id.*

As the court observed, drugs and devices are managed by two different review complexes (“Centers”) within FDA. Although each Center must ensure that the products it regulates are safe and effective for their intended uses, each was – in this instance – applying that standard in a different way. According to the court, the sponsors whose products were regulated as drugs had been “required to produce much more exhaustive scientific data demonstrating the safety and effectiveness of their ultrasound agents,” while the company whose product was regulated as a device had been “required to submit much less rigorous information and testing results.” *Id.*

For example, the Center reviewing the agents classified as drugs had required sponsors to submit extensive clinical studies demonstrating the products' safety and effectiveness in human subjects. *See id.* at 24-25. The Center reviewing the agent classified as a device required fewer and smaller studies, including at least one study conducted in animal, rather than human, subjects. The plaintiffs argued that this disparate treatment imposed "considerably greater financial and other burdens" on those companies whose products were being regulated as drugs. *Id.* 24-25.<sup>5</sup>

The *Bracco* court immediately enjoined FDA's work as to all of the products until the agency could reconcile the differences and regulate the products in a consistent manner. *See id.* at 30-31. In the words of the court, "[t]he disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious." *Id.* at 28.

**2. All fluticasone propionate nasal spray products are subject to the same statutory standard regarding product quality**

FLONASE, and any proposed generic versions of FLONASE, are similarly situated and functionally indistinguishable for purposes of establishing the quality of the respective products. Although applications for such products will be reviewed by different review offices within FDA's Center for Drug Evaluation and Research, it is incumbent upon FDA to apply the applicable legal standard for product quality in a consistent manner.

To be sure, the legal standards applicable to innovator and generic drug products differ in several critical respects. Foremost, sponsors of innovator products must independently establish the safety and effectiveness of their products, while generic sponsors rely on bioequivalence and other indicia of "sameness" to establish safety and effectiveness. *Compare* 21 USC § 355(b)(1) *with* 21 USC § 355(j)(2)(A).

That said, the law does not differentiate between innovator and generic drugs with respect to product quality. Generic sponsors must demonstrate that their products are manufactured to the same level of quality as the comparable

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<sup>5</sup> Plaintiff Bracco Diagnostics also argued to the court that it was required to collect safety data at 24, 48, and 72 hours, while the device company only had to collect such data at 48 hours; that its studies had to be conducted on a blinded basis, while FDA permitted the device company to use an open label design; and that it had to verify the results against a more difficult control than the device company. *See Bracco*, 963 F. Supp. at 24-25.

innovator drug. See FDA White Paper: *New FDA Initiative on 'Improving Access to Generic Drugs'* (June 12, 2003) (stating that generic sponsors must show that their products "are manufactured to the same quality standards" as brand-name drugs). In the words of the Director of the Office of Generic Drugs, "[t]he standards for quality are the same for brand name and generic products." *FDA Ensures Equivalence of Generic Drugs*, at [www.fda.gov/cder/about/whatwedo/testtube-17.pdf](http://www.fda.gov/cder/about/whatwedo/testtube-17.pdf) (Aug. 2002).<sup>6</sup>

On this point, the FDCA could not be clearer. For an innovator drug product, the agency must refuse to approve an NDA if "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, *quality*, and purity . . . ." 21 USC § 355(d)(3) (emphasis added). For a generic drug, the agency must refuse to approve an ANDA if "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, *quality*, and purity . . . ." *Id.* at § 355(j)(4)(A) (emphasis added). The statute plainly holds innovator and generic sponsors to the identical legal standard for assuring the quality of their products.

This fundamental proposition is reinforced in several respects. First, innovator and generic drugs are subject to the same adulteration standards under the FDCA, which provide that a drug is adulterated if, among other things, it fails to meet the level of quality that it purports or is represented to possess. See *id.* at §§ 351(a)(2)(B), (b), and (c). Second, all innovator and generic drugs are, by regulation, required to submit the same premarket information with respect to product quality. Compare 21 CFR § 314.50(d)(1) with 21 CFR § 314.94(a)(9). And third, all generic drugs that purport to be pharmaceutically equivalent to an innovator drug must be shown to meet "the identical compendial or other applicable standard of identity, strength, *quality*, and purity . . . ." *Id.* at § 320.1(c) (emphasis added); accord *Orange Book* at Preface 1.2.

In short, innovator and generic drugs are "similarly situated" with respect to product quality. They are subject to the identical legal standard. Even more, a generic drug that purports to be the same as an innovator drug must meet the same standard of quality as that drug. As FDA has explained time and again: "What is a generic drug? A copy of a brand-name drug, which must have the: *same quality*[,] same safety[,] same strength [as that drug]." *What You Want to Know*

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<sup>6</sup> The agency has expressly recognized this in the context of combination products, stating: "To achieve consistency, FDA will treat like combination products similarly." Draft Guidance for Industry and FDA: *Current Good Manufacturing Practice for Combination Products* (Sept. 2004) at 3.

*About Generic Drugs*, at [www.fda.gov/cder/present/pas/FieldPAS\\_files/FieldPAS.ppt](http://www.fda.gov/cder/present/pas/FieldPAS_files/FieldPAS.ppt) (emphasis added).

**3. FDA must apply the statutory standard of quality in an even-handed manner to all fluticasone propionate nasal spray products**

In *Bracco*, the sponsors of similar products – subject to nearly identical statutory standards – argued that they were being asked to produce different data sets to support their products. The court agreed and immediately enjoined FDA from reviewing or approving the products. The same principles would apply with equal force here, were FDA to approve generic fluticasone propionate nasal spray products that have not been shown to meet specifications for DSD and SP comparable to those that were required for FLONASE under S-019.

A generic drug product need not be manufactured in the same way as the innovator, nor must it necessarily meet identical manufacturing specifications. However, a generic drug that purports to be the same as an innovator must be manufactured to meet *the same level of quality* as that of the innovator. See 69 FR 18727, 18748-49 (Apr. 8, 2004) (stating that the specifications approved in different applications for the same drug need not be identical, but that in all cases, the approved specifications must be “adequate to ensure and preserve the . . . quality . . . of the drug”). In the case of fluticasone propionate nasal spray products, the quality of the product is dependent on the product’s DSD and SP and, specifically, on achieving consistency (*i.e.*, acceptably low variability) for these parameters.

As discussed in section II.C., above, GSK has worked assiduously over the last four years, in close consultation with the Division, to establish markedly tightened specifications for FLONASE with respect to DSD and SP. This required that GSK – at the Division’s urging – work with its supplier to modify the actuator to reduce the variability of DSD and SP performance, to a level that the agency would find acceptable.<sup>7</sup>

For example, in its first Approvable Letter, the Division objected to lack of consistency in GSK’s DSD data, as reflected in variable % RSD from data set to data set, and instructed GSK to propose tighter specifications for DSD and SP. GSK complied, revising its analytical methodology and proposing tighter

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<sup>7</sup> Note that while GSK has exclusive rights in parts and know-how developed as a result of the research and development collaboration with its supplier, that relationship does not preclude other sponsors from working with that supplier, or with any other suppliers, to develop their own high-performing product components or to otherwise improve the quality of their products.

specifications. The Division was not satisfied, and instructed GSK further to reduce inter- and intra-batch variability and to propose tighter specifications. GSK complied again, only to receive a Not Approvable Letter from the Division, requiring even tighter specifications. *See supra* at section II.C.

In the end, GSK was able to meet FDA's expectations by reducing variability in the DSD and SP parameters, as reflected in reductions in % RSD. Technical experts from GSK and its supplier worked methodically to identify and eliminate the main sources of variability in FLONASE's DSD and SP testing results. Significant changes were made to the product, resulting from considerable, painstaking work on the part of GSK and its supplier. *See supra* at section II.C.; Declaration of Robin Morrison.

Moreover, it is clear that the Division considered tight DSD and SP specifications to be central to product quality. As the Not Approvable Letter indicates, FDA's provisional view, pending additional improvements to FLONASE, was that GSK had failed, within the meaning of section 505(d) of the FDCA, to demonstrate methods of manufacturing and controls adequate to ensure product quality. The Division's letter cited inadequate DSD acceptance criteria and unacceptable SP specifications as "deficiencies" that made the supplement "not approvable under section 505(d) of the [FDCA] and 21 CFR 314.125(b)." *Supra* at section II.C.

Having determined that tight specifications for, and low variability of, DSD and SP are essential to the quality of the product, FDA must now apply this standard to all similarly situated products. A generic product that purports to be the same as FLONASE is, without question, similarly situated for purposes of the Administrative Procedure Act. Having required GSK, at significant expense and effort, to meet these new standards with regard to a product already on the market, FDA certainly must apply the same rigor to similarly situated products seeking approval.

**B. In a Closely Related Context, FDA Committed to the Application of Uniform Product Quality Standards, Which in This Case are Established in the FLONASE NDA**

In circumstances markedly similar to those presented here, FDA expressly recognized that generic products must be held to the same quality standards as the innovator products to which they are compared. Indeed, the governing law requires no less. In this case, the relevant quality standards are established in the FLONASE NDA.

Compendial standards set by the United States Pharmacopeia (“USP”) generally serve to ensure the identity, strength, quality, and purity of marketed drug products. *See* 21 USC § 351(b); 21 CFR § 299.5. The tests and assays published by the USP are recognized as valid methods for assuring product quality. In the case of fluticasone propionate nasal spray, however, the USP has yet to publish product-specific standards.

As a result, FDA has no choice but to apply the standards set within the applicable NDA to assure the identity, strength, quality, and purity of any proposed generic product. As discussed above, GSK responded to FDA’s mandate to define more exacting specifications to assure the quality of FLONASE, with particular attention to two key parameters, DSD and SP. Through a series of Approvable and Not Approvable Letters, FDA held GSK to ambitious targets, to achieve a level of consistent product quality even higher than had previously characterized the product. FDA specifically asked GSK to work with its parts supplier to further reduce variability in the DSD and SP performance of the product. Ultimately, GSK achieved a level of consistency and precision that FDA found acceptable.

The standards developed by GSK, and now approved by FDA, define a level of quality for FLONASE that must be applied to all products that purport to be the same as FLONASE. *See* 21 USC § 351(c) (a drug is adulterated if its quality differs from that which it purports or is represented to possess). As FDA has stated on numerous occasions, a generic drug product is one that has, among other things, “the same quality” as the reference listed drug product. *See supra* at section III.A.; *see also* 21 CFR § 320.1(c) (requiring that pharmaceutical equivalents must, among other things, meet the identical standard of quality). In short, FDA must ensure that other products are held to the same rigorous standards of quality as those now established under the FLONASE NDA.<sup>8</sup>

The issue of uniform product quality standards for respiratory products is not one of first impression. In the early 1990s, in the face of apparent unevenness in the standards of product quality applied to GSK’s unit dose albuterol

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<sup>8</sup> Recent comments by a senior agency official reflect the fact that specifications developed by an innovator sponsor often establish standards applicable to subsequent generic products. As the Director of FDA’s Office of Pharmaceutical Science recently recognized, “we find ourselves often in these situations where we’re held to these really tight specifications that are really hard to meet and probably have really no scientific underpinnings.” FDA Week, *Generics May Get Leeway on Some Strict Manufacturing Specifications* (Nov. 5, 2004) (attached at Tab C). In the case of FLONASE, the DSD and SP specifications were developed at the urging of the agency, and driven by the scientific demands of the Division.

sulfate inhalation product and a generic copy, GSK raised its concerns about quality discrepancies in correspondence addressed to Carl Peck, M.D., then Director of CDER. Dr. Peck agreed that GSK had raised legitimate concerns, noting that:

Our goal is to achieve substantial uniformity of standards and consistency of review among the various review divisions and across offices within the Center. Communication between scientific professionals directly involved in the review process is a key element in achieving this goal. The concerns identified in your letters have sensitized the review staff to the critical need for scientific exchange between the Offices.

Letter dated Oct. 7, 1992, from C. Peck to R. Curnow, GSK at 1 (attached at Tab D); *see also* Citizen Petition Response, Docket No. 1994-0139 (1996) (emphasizing that Dr. Peck's letter "addressed primarily uniformity and consistency of chemistry, manufacturing, and control standards among different review divisions and offices within the Center for Drug Evaluation and Research").

When, at FDA's behest, GSK began its extensive efforts to improve the quality of its nasal spray products, it had every expectation that the standards being established would be applied uniformly and consistently to all products. Dr. Peck had promised no less. The agency must now uphold that commitment.

Further, for parameters such as DSD and SP, it is not adequate for FDA to rely on bioequivalence test results as a surrogate for product quality standards. Product quality testing and BE testing serve different purposes, and are not interchangeable. *See supra* at section II.B. Only by demonstrating compliance with quality control specifications of comparable rigor to those applicable to the innovator product – including those for DSD and SP – can the sponsor of a generic nasal spray product meet the statutory requirement of manufacturing methods and controls that are adequate to ensure and preserve product quality. *See* 21 USC §§ 355(d), 355(j)(4)(A).<sup>9</sup>

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<sup>9</sup> This is not the case of an innovator seeking competitive advantage by claiming to use a higher standard that is, in fact, "merely different." 44 FR 2932, 2940 (Jan. 12, 1979). Here, FDA instigated quality enhancements, guiding GSK in the development of standards for DSD and SP and, through a series of Approvable and Not Approvable Letters, pressing GSK to set demanding specifications.

#### IV. CONCLUSION

The newly approved specifications for FLONASE, which were established only after more than four years' effort and significant changes to the product's components, constitute a standard of quality for all fluticasone propionate nasal spray products. FDA must impose the same degree of scientific, manufacturing, and quality control rigor on all products that purport to be the same as FLONASE. In so doing, the agency must ensure that all proposed generic products achieve DSD and SP performance, as reflected by % RSD figures, at the same level of quality as FLONASE. To proceed in any other manner would be arbitrary, capricious, and contrary to fundamental principles of administrative law.

V. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR § 25.31.

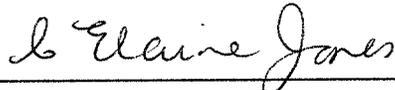
VI. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

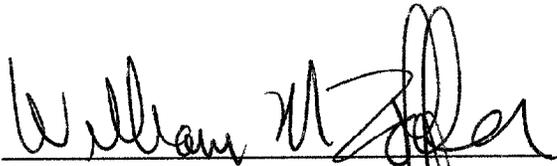
VII. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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William M. Zoffer  
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