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PATENT CERTIFICATION

U.S. Patent No.: 5,776,433

Date of Patent: July 7, 1998

Patent Title: Flunisolide Aerosol Formualtions

Patent Type: Drug Product

Patent Owner: Minnesota Mining and Manufacturing Company

The undersigned delcares that Patent No. 5,776,433 relates to pharmaceutical solution aerosol formulations wherein the propellant comprises 1,1,1,2-tetrafluoroehtane or 1,1,1,2,3,3,3-heptafluoropropane. This patent also relates to pharmaceutical aerosol formulations containing flunisolide. Flunisolide HFA Inhaler System, and aerosol formulation containing flunisolide, is the subject of this application for which approval is being sought.

Karen R. Fleschman
Karen R. Fleschman, PhD
Assistant Director, Regulatory Affairs
Forest Laboratories, Inc.

Date: 3-Apr-00

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United States Patent [19][11] Patent Number: **5,776,433**

Tzou et al.

[45] Date of Patent: **Jul. 7, 1998**[54] **FLUNISOLIDE AEROSOL FORMULATIONS**

5,695,473 12/1997 Purewal et al. 424/45

[75] Inventors: Tsi-Zong Tzou, Lake Elmo; Robert K. Schultz, Edina; Danna L. Ross, Pine Springs, all of Minn.

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[21] Appl. No.: **456,029**[22] Filed: **May 31, 1995****Related U.S. Application Data**

[63] Continuation of Ser. No. 170,509, Dec. 20, 1993, abandoned.

[51] Int. Cl.⁶ **A61K 9/12**[52] U.S. Cl. **424/45; 424/46**[58] Field of Search **424/45, 46; 514/958, 514/959****OTHER PUBLICATIONS**

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Primary Examiner—Raj Bawa
 Attorney, Agent, or Firm—Ted K. Ringsred

[57] **ABSTRACT**

Pharmaceutical aerosol formulations substantially free of chlorofluorocarbons and comprising a therapeutically effective amount of flunisolide in solution with ethanol and a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof are used for the treatment of bronchial asthma. The formulation may be delivered by a metered dose inhaler with a canister that is inert to flunisolide.

19 Claims, No Drawings

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FLUNISOLIDE AEROSOL FORMULATIONS

This is a continuation of application Ser. No. 08/170,509 filed Dec. 20, 1993, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to pharmaceutical aerosol formulations. In another aspect this invention relates to pharmaceutical solution aerosol formulations wherein the propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. In another aspect this invention relates to pharmaceutical aerosol formulations containing flunisolide.

2. Description of the Related Art

Flunisolide (6 α -fluoro-11 β , 16 α , 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone) is an antiinflammatory steroid. NASALIDE™ Nasal Solution (Syntex Laboratories, Inc.) is a flunisolide formulation for administration as a spray to the nasal mucosa (e.g., for topical rhinitis treatment). It contains flunisolide in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water, with sodium hydroxide and/or hydrochloric acid added to adjust the pH to approximately 5.3. AEROBID™/AEROBID-M Inhaler (Forest Pharmaceuticals, Inc.) is a metered dose aerosol system containing a microcrystalline suspension of flunisolide as the hemihydrate in CFC propellants (trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane) with sorbitan trioleate as a dispersing agent. AEROBID-M also contains menthol as a flavoring agent.

Current propellant-based pharmaceutical aerosol formulations, such as the above-described AEROBID™ Inhalers, use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation. Such chlorofluorocarbons (CFCs), however, have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluorocarbon 134a (HFC 134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC 227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being more ozone friendly than many chlorofluorocarbon propellants.

SUMMARY OF THE INVENTION

Flunisolide hemihydrate has been found to have appreciable solubility in HFA 134a, HFA 227 or mixtures thereof (HFA 134a dissolves about 0.006% by weight of flunisolide hemihydrate; HFA 227 dissolves about 0.004% by weight of flunisolide hemihydrate; and a 1:1 volume to volume blend of HFA 134a and HFA 227 dissolves about 0.007% by weight flunisolide hemihydrate). This intermediate level of solubility can lead to particle size increase of the drug in a suspension formulation. It is well known that particles having a diameter of greater than about 10 μ m are not suitable for inhalation to the lung. Therefore particle size increase can threaten the utility of a pharmaceutical aerosol formulation.

The present invention provides a solution aerosol formulation comprising a therapeutically effective amount of flunisolide, a propellant comprising a hydrofluorocarbon

selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof, and ethanol in an amount effective to solubilize the flunisolide in the formulation.

The present invention also provides a method of treating bronchial asthma, comprising administering via inhalation an amount of the formulation as described above effective to treat bronchial asthma.

The use of a solution formulation of the invention eliminates the problems associated with an increase of particle size. This invention also eliminates other problems encountered with suspension aerosols such as rapid flocculation, irreversible particle aggregation and bulk separation (creaming or settling); all of which affect dose uniformity. Moreover a formulation of the invention provides a higher respirable fraction of drug than does the currently available suspension aerosol formulation of flunisolide based on CFC propellants.

DETAILED DESCRIPTION OF THE INVENTION

All weight percentages recited herein are based on the total weight of the formulation unless otherwise indicated.

The medicament flunisolide is known and disclosed, e.g., in U.S. Pat. No. 4,933,168 (Jones et al.). Flunisolide is generally present in a formulation of the invention in a therapeutically effective amount, i.e., an amount such that one or more metered volumes of the formulation when delivered to the lung by oral or nasal inhalation contains an amount of medicament effective to exert the intended therapeutic action. Preferably the medicament constitutes about 0.1 to about 0.9 percent by weight, more preferably about 0.2 to about 0.6 percent by weight of the total weight of the formulation.

The formulation of the invention is a solution formulation, i.e., the flunisolide is substantially fully dissolved in the formulation and the formulation is substantially free of undissolved flunisolide. Flunisolide has been known to exist in several polymorphic forms. A formulation of the invention, however, contains flunisolide but not a particular polymorphic form thereof, as such polymorphic forms lose their crystalline identity when in solution. Therefore this invention avoids complications that can occur in certain suspension steroid formulations due to in situ changes in crystal form (e.g., crystal polymorphism). Also any appropriately soluble polymorphic form of flunisolide (e.g., flunisolide hemihydrate) can be used in preparing a formulation of the invention.

A formulation of the invention contains ethanol in an amount effective to solubilize the flunisolide in the formulation. Preferably the ethanol constitutes about 3 to about 30 percent by weight of the total weight of the formulation. More preferably, ethanol constitutes about 10 to about 20 percent by weight of the aerosol formulation.

The hydrofluorocarbon propellant can be 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or a mixture thereof in any proportion. The propellant is present in an amount sufficient to propel a plurality of doses from an aerosol canister such as a metered dose inhaler. The propellant preferably constitutes from about 68 to about 97 percent by weight, and more preferably from about 75 to about 87 percent by weight of the total weight of the aerosol formulation. The formulations of the invention are preferably free of chlorofluorocarbon propellants such as fluorotrichloromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane. Most preferably, the hydrofluoro-

carbon propellant is the only propellant present in the formulations of the invention.

A formulation of the invention can contain suitable excipients (e.g., those disclosed in U.S. Pat. No. 5,225,183, Purewal, et al.) in amounts readily determined by those skilled in the art. Certain excipients, e.g., certain surfactants, flavoring agents, and/or water, are beneficial to some embodiments of the invention. For example, it has been found that the chemical stability of certain formulations of the invention (that is, stability of the formulation to degradation of flunisolide) is enhanced by the presence of water. When water is included in a formulation of the invention it will generally be present in an amount of about 0.005 percent to about 1 percent by weight of the total weight of the formulation.

It has also been found that the chemical stability of certain formulations of the invention is enhanced by the presence of sorbitan trioleate. When sorbitan trioleate is included in a formulation of the invention it will generally be present in an amount of about 0.001 percent to about 0.1 percent by weight of the total weight of the formulation.

It has also been found that the chemical stability of certain formulations of the invention is enhanced by the presence of cetylpyridinium chloride. When cetylpyridinium chloride is included in a formulation of the invention it will generally be present in an amount of about 0.001 percent to about 0.2 percent by weight of the total weight of the formulation.

Formulations of the invention optionally further comprise a flavoring agent. A preferred flavoring agent is menthol. In an embodiment of the invention comprising menthol, menthol is preferably present in an amount effective to mask the taste of flunisolide when an aerosolized dose of the formulation is inhaled orally, e.g., about 0.3 percent by weight of the total weight of the formulation.

Formulations of the invention can be prepared by either pressure filling or cold filling techniques, both of which are well known to those skilled in the art. Ethanol and the excipient or excipients, if any, are combined with the propellant and then this solution is pressure filled or cold filled into aerosol vials containing the flunisolide. Alternatively, the flunisolide and any non-volatile excipients are dissolved in ethanol in an aerosol vial. The aerosol vial is then fitted with a valve and pressure filled with the propellant.

Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular excipients used (if any), on the propellant, and on the medicament being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional chlorofluorocarbon (CFC) formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. Moreover, conventional CFC formulations generally contain a surfactant or lubricant. Some formulations of the invention, however, do not contain a surfactant or a lubricant. Therefore certain formulations of the invention are preferably dispensed via a valve assembly wherein the diaphragm is fashioned by extrusion, injection molding or compression molding from a thermoplastic material such as FLEXOMER™ GERS 1085 NT polyolefin (Union Carbide). Another suitable valve rubber is a nitrile rubber ("DB-218") available from American Gasket and Rubber, Schiller Park, Ill.

Conventional aerosol canisters can be used to contain a formulation of the invention. It has been found, however, that certain containers enhance the chemical stability of certain formulations of the invention and/or minimize the absorption of flunisolide onto the container walls; therefore, it is preferred to contain a formulation of the invention within a glass aerosol vial or an aluminum aerosol vial having an interior formulation chamber coated with a resin that is inert to flunisolide and preferably does not absorb flunisolide from the formulation. Suitable resins for coating the formulation chamber include materials commonly employed as interior can coatings, such as epoxy resins (e.g., epoxy-phenolic resins and epoxy-urea-formaldehyde resins).

A formulation of the invention can be administered to the lung by oral or nasal inhalation. Oral inhalation is preferred, and conventional actuators for oral inhalation can be used in connection with a formulation of the invention. Particle size or droplet size of the inhaled dose is important to an inhalable dose form intended to be administered to the lung. Particle size or droplet size and respirable fraction of a propellant based solution aerosol formulation can be affected by the size of the orifice through which the formulation passes. It is preferred to administer a formulation of the invention through an actuator having an orifice diameter of about 0.25 mm (0.010 inch). An example of such an actuator is actuator model M3756, 3M Company.

The examples set forth below are intended to illustrate the invention.

Respirable Fraction

In this assay the respirable fraction (the percent by weight of particles having an aerodynamic particle size of less than 4.7 μ m) of the aerosol formulation is determined using an Anderson Cascade Impactor (available from Anderson Sampler Inc.; Atlanta, Ga.).

The aerosol vial containing the formulation to be tested is primed 5 times. The valve and valve stem are then cleaned with ethanol and dried with compressed air or nitrogen. The aerosol vial and a clean, dry actuator (Model M3756, 3M) are coupled to the glass throat attached to the top of the impactor using an appropriate firing adaptor. The calibrated vacuum pump (28.3 L/min) attached to the impactor is turned on. The vial is actuated. After the aerosol cloud has disappeared (about 4 seconds), the vial and actuator are disconnected, shaken for about 10 seconds, then reconnected to the throat and actuated again. This procedure is repeated until the vial has been actuated a total of 10 times. The cascade impactor is disassembled and each component is rinsed with diluent. Each solution is analyzed for flunisolide content using high performance liquid chromatography or ultraviolet spectroscopy (241 nm). The respirable fraction is calculated as follows:

$$\% \text{ Respirable} = \frac{\text{Flunisolide recovered from plates 3-7}}{\text{Flunisolide recovered from the throat, 0 jet stage and plates 0-7}} \times 100$$

Percent Degradation Impurities and Percent Drug Recovery

In this assay the percent of degradation impurities and the percent of drug recovered is determined using high performance liquid chromatography.

Sample Solution Preparation

The aerosol vial containing the formulation to be assayed is weighed then chilled in dry ice for 20 minutes. The cap is removed and the contents of the vial are poured into a pre-chilled volumetric flask (100 mL). The propellant is allowed to evaporate. The cap and vial are rinsed with

acetonitrile into the volumetric flask. The flask is brought to volume with ethanol or preferably acetonitrile. A portion (2 mL) of this solution is pipetted into a volumetric flask (100 mL) and the flask is brought to volume with mobile phase (The mobile phase is prepared by combining glacial acetic acid (10 mL) with distilled water (990 mL) and combining a portion (650 mL) of the resulting solution with acetonitrile (350 mL)).

Standard Solution Preparation

Flunisolide hemihydrate (about 32 mg) is placed into a volumetric flask (50 mL) then dissolved in ethanol or preferably acetonitrile. The flask is brought to volume with ethanol or preferably acetonitrile. A portion (2 mL) of this solution is pipetted into a volumetric flask (100 mL) and the flask is brought to volume with mobile phase.

Procedure

A portion (25 μ L) of the standard solution is injected into the HPLC (flow rate: 2.0 L/min; column μ -Bondpak C18 (Waters) 30 cm by 3.9 mm; mobile phase as described above; UV detector set at 254 nm) and the recorder sensitivity is adjusted to produce peaks at 70-90% of full scale. The chromatogram is obtained and the peak areas are measured. This chromatogram provides a correlation between the weight of flunisolide and the area of the flunisolide peak. It also provides the peak areas of any impurities which may be present in the raw drug (flunisolide hemihydrate) prior to formulation.

A portion (25 μ L) of the sample solution is injected into the HPLC under the same conditions as the standard. The chromatogram is obtained and the peak areas are measured. Calculation of Percent Degradation Impurities

The percent impurities in the raw drug is determined using the peak areas from the chromatogram of the standard solution and the equation below.

$$\% \text{ impurities in raw drug} = \frac{\text{Sum of the areas of the impurity peaks}}{\text{Sum of the areas of the impurity peaks and the flunisolide peak}} \times 100$$

The percent impurities in the sample is obtained by performing the same calculation on the peak areas from the sample chromatogram.

The percent degradation impurities is then determined using the equation below.

$$\% \text{ degradation impurities} = \frac{\% \text{ impurities in the sample}}{\% \text{ impurities in raw drug}}$$

Percent Drug Recovery

This calculation is based on the amount of flunisolide in the sample vial before and after storage.

The amount of flunisolide that was in the aerosol vial after storage is determined using the area of the flunisolide peak from the sample chromatogram and the correlation between weight of flunisolide and the area of the flunisolide peak that is obtained from the standard chromatogram.

The amount of flunisolide that was in the aerosol vial when it was first prepared is known.

The percent drug recovery is then determined using the equation given below.

$$\% \text{ drug recovery} = \frac{\text{amount of flunisolide after storage}}{\text{initial amount of flunisolide}} \times 100$$

EXAMPLE 1

Flunisolide hemihydrate (60 mg) and ethanol (2.25 g) were placed in a 10 mL aluminum aerosol vial. The vial was

cooled to about -78° C. in a dry ice/trichloromethane bath then filled with cold P134a (1.1.1.2-tetrafluoroethane, 12.75 g). The vial was sealed with a 50 μ L metered dose valve having a diaphragm of DB-218 nitrile rubber (American Gasket and Rubber, Schiller Park, Ill.). The respirable fraction was determined using the test method described above and found to be 55%.

EXAMPLE 2

Flunisolide hemihydrate (61.2 mg) and ethanol (2.25 g) were placed in a 10 mL aluminum aerosol vial. The vial was sealed with a continuous valve then pressure filled with P227 (1.1.1.2.3.3.3-heptafluoropropane, 14.55 g). The vial was chilled then the continuous valve was replaced with a 50 μ L metered dose valve having a diaphragm of DB-218 nitrile rubber (American Gasket and Rubber, Schiller Park, Ill.). The respirable fraction was determined using the method described above and found to be 43%.

EXAMPLE 3

A bulk propellant solution was prepared by dissolving oleic acid (0.0394 g) and menthol (0.38423 g) in ethanol (19.427) in a 4 ounce (120 mL) glass aerosol vial. A continuous valve onto the vial and then pressure filling with 1.1.1.2-tetrafluoroethane (109.6 g). Flunisolide hemihydrate (about 62 mg each) was placed into 10 mL aluminum aerosol vials which were then sealed with continuous valves that were fitted with gaskets and diaphragms made from FLEXOMER™ GERS 1085 NT polyolefin (Union Carbide). The vials were pressure filled with the bulk propellant solution via a valve to valve transfer button to provide a formulation containing 0.4 percent by weight of flunisolide, 0.03 percent by weight of oleic acid, 0.3 percent by weight of menthol and 15 percent by weight of ethanol. The vials were stored at 40° C. and 85% relative for humidity for 3 weeks then assayed according to the test method described above for percent degradation impurities and percent drug recovery. The results are shown in Table 2 below where each value is the average of 2 separate vials.

EXAMPLES 4-14

Using the general method of Example 3, the aerosol formulations shown in Table 1 below were prepared. Each formulation contained 0.4 percent by weight of flunisolide and 15 percent by weight of ethanol. The percentages in Table 1 are by weight based on the total weight of the formulation. The vials were stored at 40° C. and 85% relative humidity for the time indicated in Table 2 then assayed for percent degradation impurities and percent drug recovery. The results are shown in Table 2 below where, unless otherwise indicated, each value is the average of 2 separate vials.

TABLE 1

Example Number	Propellant	Excipient (s)
4	134a	None
5	227	None
6	134a	0.03% oleic acid
7	227	0.03% oleic acid
8	134a	0.3% menthol
9	227	0.3% menthol
10	227	0.3% menthol/0.03% oleic acid
11	134a	0.002% Span 85
12	227	0.002% Span 85

TABLE 1-continued

Example Number	Propellant	Excipient (s)
13	134a	0.3% menthol/0.002% Span 85
14	227	0.3% menthol/0.002% Span 85

¹Sorbitan trioleate; Atlas Chemical Inc.

TABLE 2

Example Number	Weeks Stored	% Degradation Impurities	% Drug Recovery
3	3	2.58	95.4
4	3	5.97	93.1
5	3	1.20	98.7
6	3	3.89	94.5
7	3	2.38	96.4
8	3	1.18	97.3
9	3	0.88	97.9
10	3	1.54	97.5
11	5	1.77 ¹	99.7 ¹
12	5	1.52 ¹	98.1 ¹
13	5	2.63 ¹	98.4 ¹
14	5	2.09 ¹	98.6 ¹

¹Value obtained from a single vial

EXAMPLES 15-18

Using the general method of Example 3, the aerosol formulations shown in Table 3 below were prepared. Each formulation contained 0.4 percent by weight of flunisolide. The percentages in Table 3 are by weight based on the total weight of the formulation. The vials were stored at 40° C. and 85% relative humidity for 3 weeks then assayed for percent degradation impurities and percent drug recovery. The results are shown in Table 4 below where each value is the average of 2 separate vials.

TABLE 3

Example Number	Propellant	Excipients
15	134a	0.75% water/14.25% ethanol
16	227	0.75% water/14.25% ethanol
17	134a	0.3% menthol/0.75% water/ 14.25% ethanol
18	227	0.3% menthol/0.75% water/ 14.25% ethanol

TABLE 4

Example Number	% Degradation Impurities	% Drug Recovery
15	0.63	97.5
16	0.65	96.9
17	0.69	95.4
18	0.53	95.6

EXAMPLE 19

Using the general method of Example 3 except that both glass and aluminum aerosol vials were used, a formulation containing 0.4 percent by weight flunisolide, 15 percent by weight ethanol and P227 was prepared. The vials were stored at 40° C. and 85% relative humidity for the number of weeks indicated in Table 5 then assayed for percent

degradation impurities and percent drug recovery. The results are shown in Table 5 below where each value is the average of 2 separate vials.

TABLE 5

Vial Type	Weeks	% Degradation Impurities	% Drug Recovery
aluminum	3	1.91	96.6
aluminum	8	4.63	94.0
glass	3	0.84	98.8
glass	8	1.73	99.7

EXAMPLE 20

Using the general method of Example 3 except that both glass and aluminum aerosol vials were used, a formulation containing 0.4 percent by weight flunisolide, 0.3 percent by weight menthol, 15 percent by weight ethanol and P227 was prepared. The vials were stored at 40° C. and 85% relative humidity for the number of weeks indicated in Table 6 then assayed for percent degradation impurities and percent drug recovery. The results are shown in Table 6 below where each value is the average of 2 separate vials.

TABLE 6

Vial Type	Weeks	% Degradation Impurities	% Drug Recovery
aluminum	3	2.04	96.1
aluminum	8	4.49	94.7
glass	3	0.81	98.4
glass	8	1.52	97.1

EXAMPLES 21-28

A set of aerosol formulations containing 0.43 percent by weight of flunisolide, 15 percent by weight of ethanol, P227 and various excipients was prepared using the following method. A bulk propellant solution was prepared by placing the excipient and ethanol in a 4 ounce (120 mL) glass bottle, sealing the bottle with a continuous valve and then pressure-filling with P227. The bottle was cooled to -60° C., the continuous valve was removed and the bulk propellant solution was poured into chilled aluminum aerosol vials containing a preweighed amount of flunisolide hemihydrate. The vials were sealed with blind ferrules that were equipped with gaskets made from FLEXOMER™ GERS 1085 NT polyolefin. The identity and amount of excipient present in each formulation is shown in Table 7 below where the percentages are by weight based on the total weight of the formulation. The vials were stored for four weeks at either 40° C. and ambient humidity or at 40° C. and 85% relative humidity then assayed for percent degradation impurities and percent drug recovery. The results are shown in Table 7 where each value is the average of eight separate vials, four under each storage condition.

TABLE 7

Example Number	Excipient (s)	% Degradation Impurities	% Drug Recovery
21	None	2.18	97.2
22	0.2% CPC ¹	1.41	98.2
23	0.048% Span 85 ²	1.78	98.1

TABLE 7-continued

Example Number	Excipient (s)	% Degradation Impurities	% Drug Recovery
24	0.048% Span 85/ 0.2% CPC	1.39	99.1
25	0.1% oleic acid	7.41	89.9
26	0.1% oleic acid/ 0.2% CPC	4.54	93.0
27	0.1% oleic acid/ 0.048% Span 85	5.97	92.3
28	0.1% oleic acid/0.2% CPC/0.048% Span 85	3.89	93.4

¹CPC is cetylpyridium chloride²Sorbitan trioleate; Atlas Chemical Inc.

EXAMPLE 29

A bulk propellant solution containing 15 percent by weight of ethanol in P227 was prepared according to the method of Example 21. This solution was cold filled under nitrogen into four different types of aerosol vials which were chilled and contained a preweighed amount of flunisolide hemihydrate. The final formulation contained 0.43 percent by weight of flunisolide. The vials were sealed with blind ferrules equipped with gaskets prepared from FLEXOMER™ GERS 1085 NT polyolefin. The vials were stored at 40° C. and 85% relative humidity for 5 weeks then assayed for percent degradation impurities and percent drug recovery. The results are shown in Table 8 below where each value is the average of 2 separate vials.

TABLE 8

Vial Type	% Degradation Impurities	% Drug Recovery
aluminum ¹	2.07	99.8
plastic ²	0.27	23
epoxy coated aluminum ³	0.14	100.6
glass ⁴	1.07	100.1

¹Available from 3M Company²Made from polyethylene terephthalate and are available from Precise Plastic Ltd., United Kingdom³Epoxy/phenol-formaldehyde resin coated aluminum vials, coated by Cebal⁴Made from Type-III (soda-lime) glass and are available from Wheaton Coated Products

What is claimed is:

1. A solution aerosol formulation consisting essentially of about 0.1 percent to about 0.9 percent by weight of flunisolide in solution; a propellant comprising a hydrofluorocarbon propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof; about 3 percent to about 30 percent by weight and ethanol in an amount effective to solubilize the flunisolide in the formulation.

2. An aerosol formulation according to claim 1, wherein the propellant comprises 1,1,1,2-tetrafluoroethane.

3. An aerosol formulation according to claim 1, wherein the propellant comprises 1,1,1,2,3,3,3-heptafluoropropane.

4. An aerosol formulation according to claim 1, wherein the propellant comprises a mixture of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane.

5. An aerosol formulation according to claim 1, characterized in that it is free of chlorofluorocarbon propellants.

6. An aerosol formulation according to claim 1 further comprising about 0.005 percent to about 1 percent by weight water.

7. An aerosol formulation according to claim 1 further comprising about 0.001 percent to about 0.1 percent by weight sorbitan trioleate.

8. An aerosol formulation according to claim 1 further comprising about 0.001 percent to about 0.2 percent by weight cetylpyridinium chloride.

9. An aerosol formulation according to claim 1 further comprising a flavoring agent.

10. An aerosol formulation according to claim 1 further comprising about 0.3 percent by weight menthol.

11. An aerosol formulation according to claim 1 comprising from about 0.2 percent to about 0.5 by weight flunisolide, from about 10 to about 20 percent by weight ethanol, and 1,1,1,2,3,3,3-heptafluoropropane.

12. An aerosol formulation according to claim 11 comprising from about 0.2 percent to about 0.5 percent by weight flunisolide, from about 10 to about 20 percent by weight ethanol and from about 0.001 percent to about 0.005 percent by weight sorbitan trioleate.

13. An aerosol formulation according to claim 1 comprising from about 0.2 percent to about 0.5 by weight flunisolide, from about 10 to about 20 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane.

14. An aerosol formulation according to claim 13 comprising from about 0.2 percent to about 0.5 percent by weight flunisolide, from about 10 to about 20 percent by weight ethanol and from about 0.001 percent to about 0.005 percent by weight sorbitan trioleate.

15. A method of treating bronchial asthma comprising administering via inhalation an amount of a formulation according to claim 1 sufficient to treat bronchial asthma.

16. A metered dose inhaler comprising: (i) an aerosol canister defining a formulation chamber; and (ii) a formulation according to claim 1, wherein said formulation is contained within said formulation chamber.

17. An inhaler according to claim 16, wherein the formulation chamber, is coated with a resin that is inert to flunisolide.

18. An inhaler according to claim 17, wherein the resin is an epoxy resin.

19. An inhaler according to claim 16, wherein the aerosol canister is glass.

* * * * *

PATENT INFORMATION
U.S. Patents

Patent No.	Title	Date of Patent	Type of Patent	Patent Owner
5,776,433	Flunisolide Aerosol Formulations	July 7, 1998	Drug Product	3M
5,980, 867	Flunisolide Aerosol Formulations	November 9, 1999	Drug Product	3M

EXCLUSIVITY SUMMARY

NDA # 21-247

SUPPL #

HFD # 570

Trade Name Aerospan (flunisolide HFA, 80 mcg) Inhalation Aerosol

Generic Name Flunisolide HFA

Applicant Name Forest Laboratories, inc.t

Approval Date, If Known January 27, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-340

Aerobid

NDA# 20-409 Nasarel

NDA# 18-148 Nasalide

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

ANC-MD-01 and ANC-MD-03

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

ANC-MD-01 under IND 51,456 & ANC-MD-03 under IND 51,456

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

ANC-MD-01 and ANC-MD-03

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 51,456 YES ! NO
! Explain:

Investigation #2
IND # 51,456 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:
N/A

Investigation #2

YES

Explain:

N/A

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: Ladan Jafari
Title: Regulatory Health Project Manager
Date: 1-27-06

Name of Office/Division Director signing form: Badrul Chowdhury, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
1/27/2006 11:29:29 AM

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CLAIMED EXCLUSIVITY

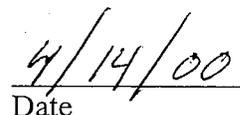
Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4), Forest Laboratories, Inc. claims 3 years exclusivity for Aerobid HFA which contains flunisolide hemihydrate as the active ingredient with hydrofluoroalkanes (HFA) as the propellant.

As set forth in 21 CFR 314.108(a), Forest Laboratories, Inc. certifies that this application contains the following new clinical investigations that were conducted by Forest Laboratories to demonstrate the safety and efficacy of Aerobid HFA and are essential to support approval of this application:

- ANC-MD-01: A Multicenter, Double-Blind, Placebo Controlled, Randomized Trial Evaluating the Safety and Efficacy of HFA Flunisolide vs. CFC Flunisolide in Patients with Mild to Moderate Asthma
- ANC-MD-02: A Long-Term, Open Label Study to Evaluate the Safety of HFA Flunisolide in Adult and Adolescent Patients with Mild to Moderate Asthma
- ANC-MD-03: A Multicenter, Double-Blind, Placebo Controlled, Randomized Trial Evaluating the Safety and Efficacy of HFA Flunisolide vs. CFC Flunisolide in Pediatric Patients with Mild to Moderate Asthma
- ANC-MD-04: A Long-Term, Open Label Study to Evaluate the Safety of HFA Flunisolide in Children with Mild to Moderate Asthma



Lester S. Gibbs, Ph.D.
Manager, Regulatory Affairs



Date

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-247 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 27, 2005 Action Date: January 27, 2006

HFD 570 Trade and generic names/dosage form: Aerospna HFA (flunisolide inhalation solution)

Applicant: Forest Therapeutic Class: Respiratory

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Asthma

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred >6 years Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0 months kg _____ mo. < 6 months yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

x Other:

Difficult to diagnose the disease in children

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min 6 months kg _____ mo. < 6 years yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

Date studies are due (mm/dd/yy): August 12, 2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min > 6 years kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-247
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
11/7/2005 11:08:20 AM

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in Original



FAX: 212-750-9752
PHONE: 212-421-7850

DEBARMENT CERTIFICATION

In compliance with Section 306(k) of the Federal Food, Drug and Cosmetic Act, we hereby certify that Forest Laboratories, Inc., did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act in connection with this application (NDA #21-247) for Flunisolide HFA Inhaler System.

FOREST LABORATORIES, INC.

A handwritten signature in cursive script, appearing to read 'L. Olanoff', written over a horizontal line.

Lawrence Olanoff, M.D., Ph.D.
Executive Vice President, Scientific Affairs

FOREST LABORATORIES, INC.
909 Third Avenue
New York, NY 10022-4731



FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Direct Line: (201) 386-2142
Fax: (201) 524-9711

January 27, 2006

Badrul Chowdhury, MD, PhD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA: 21-247 Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol
Re: Response to FDA Comments - Post Marketing Commitments

Dear Dr. Chowdhury:

Reference is made to **NDA 21-247 Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol and FDA fax on January 26, 2006 regarding post marketing study commitments**. Forest agrees to the following two post marketing study commitments:

1. To conduct a study to comprehensively address device durability and reliability.

Ideally, in all Phase 2 and 3 studies utilizing the to-be-marketed formulation, patients are asked to report devices they perceive to be broken or malfunctioning. Any device so reported is then returned and evaluated to identify the problem. Device use and performance is also evaluated through directed questions defined in the protocols. In this way, information is generated regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g. 100) of devices that are apparently functioning normally in patients' hands should be collected near the end of the life of the device and evaluated by in vitro performance testing. These evaluations were not addressed in the development program for Aerospan Inhalation Aerosol, and will be addressed as a post marketing study commitment. The dose counter reliability study to which we had agreed would not adequately address the issue of device durability. However, collection of this type of information will be incorporated into future studies.

We propose the following timeline:

Protocol Submission: June 2006
Study Start: August 2007
Final Report Submission: January 2009

- 2. To conduct a labeling comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling.**

Aerospan Inhalation Aerosol is a complex device, including a built-in spacer that makes the device unique and increases the complexity of use. In addition, the instruction that the patient should inhale within one second of actuation is quite specific, and may not be easy for the patient to comprehend. While we have developed a specific tear-off Patient Instructions for Use to instruct patients in the proper use of the device, the instructions are quite complex and are untested in the hands of the patient. In order to evaluate the utility of the labeling, we will perform a label comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling. A label comprehension study should test, for example, whether the written instructions provide sufficiently clear instructions that patients can open, inspect, use, and close the device appropriately. It should also test whether the written instructions provide sufficiently clear instructions that patients can appropriately learn to time the inhalation to actuation. Such a study may identify any problems with the device handling and use, and inform modification of the Patient Instructions for Use.

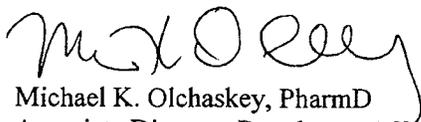
We propose the following timeline:

Protocol Submission: June 2006
Study Start: May 2007
Final Report Submission: January 2008

We propose the above studies and timelines, taken into consideration that drug supplies are not immediately available, and will be available later.

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Doreen V. Morgan at (201) 386-2131.

Sincerely,



Michael K. Olchaskey, PharmD
Associate Director, Regulatory Affairs
michael.olchaskey@frx.com

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-247	Efficacy Supplement Type SE-	Supplement Number
Drug: Aerospan HFA (flunisolide HFA) Inhalation Aerosol		Applicant: Forest
RPM: Ladan Jafari		HFD-570 Phone #301-796-1231
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> • Chem class (NDAs only) 		3
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		N/A
✓ User Fee Goal Dates		January 27, 2006
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		<input checked="" type="checkbox"/> Paid UF ID number
<ul style="list-style-type: none"> • User Fee waiver 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	06/13/2000, 04/23/2001, 07/24/2003, 1/27/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Completed on 11/07/2005
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	03/02/2001, 01/09/2006
❖ Biopharmaceutical review(s) (indicate date for each review)	04/26/2001, 06/05/2002
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	03/08/2001
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	05/03/2001, 06/05/2002, 05/06/2003, 07/24/2003, 04/14/2004
Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	04/19/2001, 12/07/2001, 05/22/2002, 05/28/2003, 04/09/2004, 11/23/2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 26, 2006

To: Michael Olchaskey	Ladan Jafari
Company: Forest	From: Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-796-9728
Phone number: 201-386-2142	Phone number: 301-796-1231
Subject: NDA 21-247	

Total no. of pages including cover: 2

Comments: carton and container comments

Document to be mailed: YES NO

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NDA 21-247

Dear Mr. Olchaskey:

We are reviewing your NDA application for Aerospan and we have the following comments.

1. The following comment pertains to the boxed statements on all carton, canister, and spacer labeling:
 - a. The boxed statements on the cartons should read: "The actuator and spacer supplied with AEROSPAN™ Inhalation Aerosol should not be used with any other product canisters. Actuators from other products should not be used with an AEROSPAN canister" (instead of "...with an AEROSPAN Inhalation Aerosol").
 - b. The boxed statements on the canisters should read: "Canister to be used with AEROSPAN™ actuator only".
 - c. The statement on the spacer should read: "Use with AEROSPAN™ canister only".

2. The following comment pertains to the established and proprietary names on all carton, canister, and spacer labeling:
 - a. The established name should be of equal prominence to the proprietary name (proprietary name is bold, established name is narrow font, and not bold). We suggest you place "flunisolide HFA, 80 mcg" on a separate line from the proprietary name in order to accommodate these changes.

I may be reached at 301-796-1231 for any questions.


Ladan Jafari, Regulatory Project Manager

NDA 21-247

Drafted by: LJ/1-26-06

Initialed by: Peri/1-26-06
Chowdhury/1-26-06

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 26, 2006

To: Michael Olchaskey	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-796-9728
Phone number: 201-386-2142	Phone number: 301-796-1231
Subject: NDA 21-247	

Total no. of pages including cover: 3

Comments: stat comments

Document to be mailed: YES NO

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We have completed our review of your NDA and have the following concerns regarding the device durability and labeling.

1. Ideally, in all Phase 2 and 3 studies utilizing the to-be-marketed formulation, patients are asked to report devices they perceive to be broken or malfunctioning. Any device so reported is then returned and evaluated to identify the problem. Device use and performance is also evaluated through directed questions defined in the protocols. In this way, information is generated regarding the types and frequencies of device malfunction based on data from a large number of devices, and an analysis of the cause may lead to potential improvements to the device itself. In addition, a small number (e.g. 100) of devices that are apparently functioning normally in patients' hands should be collected near the end of the life of the device and evaluated by in vitro performance testing. These evaluations were apparently not addressed in the development program for Aerospan Inhalation Aerosol, and must be addressed as a post marketing study commitment. The dose counter reliability study to which you have agreed would not adequately address the issue of device durability. However, collection of this type of information could be incorporated into future clinical or marketing studies, if any further clinical studies are planned.
2. Aerospan Inhalation Aerosol is a complex device, including a built-in spacer that makes the device unique and increases the complexity of use. In addition, the instruction that the patient should inhale within one second of actuation is quite specific, and may not be easy for the patient to comprehend. While you have developed a specific tear-off Patient Instructions for Use to instruct patients in the proper use of the device, the instructions are quite complex and are untested in the hands of the patient. In order to evaluate the utility of the labeling, perform a label comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling. A label comprehension study should test, for example, whether the written instructions provide sufficiently clear instructions that patients can open, inspect, use, and close the device appropriately. It should also test whether the written instructions provide sufficiently clear instructions that patients can appropriately learn to time the inhalation to actuation. Such a study may identify any problems with the device handling and use, and inform modification of the Patient Instructions for Use.

In order to address these issues listed above submit post marketing study commitments as listed below.

1. A study to comprehensively address device durability and reliability.

Protocol Submission: XXX (propose date)

Study Start: XXX (propose date)

Final Report Submission: Propose a date within a three-year time frame.

2. A labeling comprehension study to ensure that patients are able to read and use the device in the manner specified in the labeling.

Protocol Submission: XXX (propose date)

Study Start: XXX (propose date)

Final Report Submission: Propose a date within a two-year time frame.

I may be reached at 301-796-1231 for any questions.



Ladan Jafari, Regulatory Health Project Manager

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NDA 21-247

Page 3

Drafted by: Barnes/1-26-06

Initialed by: Starke/1-26-06
Sullivan/1-26-06

Filename: N21247P4commitment.doc

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FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Direct Line: (201) 386-2142
Fax: (201) 524-9711

January 26, 2006

Badrul Chowdhury, MD, PhD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA: 21-247 Aerospan™ (flunisolide HFA, 80 mcg) Inhalation Aerosol
Re: Response to FDA Request - Right to Reference NDA 18-340 Aerobid® (flunisolide)

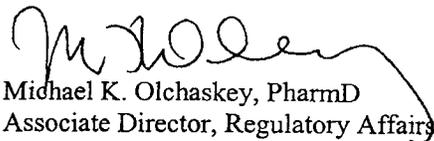
Dear Dr. Chowdhury:

Reference is made to the telephone request from Ms. Ladan Jafari on January 26, 2006 regarding the right to reference the Aerobid® NDA.

Please find enclosed the portion of the licensing agreement between Syntex and Forest that includes information that grants Forest right of reference to NDA 18-340 Aerobid® (flunisolide).

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Doreen V. Morgan at (201) 386-2131.

Sincerely,


Michael K. Olchaskey, PharmD
Associate Director, Regulatory Affairs
michael.olchaskey@frx.com

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to FDA Request - Right to Reference Aerobid NDA

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Michael K. Olchaskey, PharmD Associate Director, Regulatory Affairs	DATE: 1/26/06
---	--	------------------

ADDRESS (Street, City, State, and ZIP Code) Harborside Financial Center, Plaza III, Suite 602, Jersey City, NJ 07311	Telephone Number (201) 386-2142
---	--------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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AGREEMENT dated as of December 29th, 1995 by and between FOREST LABORATORIES, INC., a Delaware corporation having its principal executive offices at 909 Third Avenue, New York, New York 10022 ("Forest") and SYNTEX PHARMACEUTICAL INTERNATIONAL LIMITED, a Bermuda corporation having its principal executive offices at Rosebank Building 12, Bermudiana Road, Hamilton, Bermuda ("Syntex").

R E C I T A L S :

A. Syntex and Forest are parties to that certain Flunisolide Bronchial Product License Agreement dated July 9, 1982, as amended to date, including, without limitation, by letter agreements and consents dated July 28, 1982, June 25, 1986 and January 1, 1992 (collectively, the "License Agreement") and to the related Flunisolide Supply Agreement effective as of January 1, 1986 (as amended to date, the "Supply Agreement"). Forest is currently marketing a CFC aerosol formulation of flunisolide under the terms of the License Agreement under the trademark "Aerobid®" (the "Current Product"). This Agreement and the provisions hereof are not intended to and do not modify, amend or change the License Agreement or Supply Agreement with respect to the Current Product, which agreements shall remain in full force and effect in accordance with their respective terms.

B. Forest desires to develop and is engaged in the development of other pharmaceutical products, e.g. non-CFC aerosol and dry powder formulations, containing flunisolide as an active ingredient for bronchial administration. The parties

1.2. "Products" shall mean any formulated product in finished dosage form designed for inhalation therapy through bronchial administration in which an active ingredient is Flunisolide covered by any of the claims of the Patents, but excluding the Current Product.

1.3. "Patents" shall mean United States letters patent Nos. 4,273,710 and 4,933,168, including all extensions and reissues thereof.

1.4. "NDA" shall mean the New Drug Application owned by Syntex which covers the marketing of the Current Product.

1.5. "Territory" shall mean the United States of America, including its territories and possessions.

1.6. "Flunisolide", "flunisolide" or "flunisolide hemihydrate" shall mean (6 - alpha, 11 - beta, 16 - alpha) - 6 - fluoro - 11, 21 - dihydroxy - 16, 17 - [(1-methylethylidene) bis(oxy)] pregna - 1, 4 - dione - 3, 20 - dione hemihydrate.

2. Confirmation of License; NDA Matters

2.1. Syntex hereby confirms to Forest that the License Agreement grants to Forest the exclusive right and license, without the right to sublicense (except as set forth in Sections 13.1 and 13.2 thereof), under the Patents to make, have made, use and sell Products (in addition to the Current Product) in the Territory; provided, however, that the foregoing grant does not include the right to manufacture flunisolide. In consideration of the substantial research and development effort being undertaken by Forest in the development of Products, and Forest's commitment to use its best efforts to conduct research



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2006

To: Michael Olchaskey	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-796-9728
Phone number: 201-386-2142	Phone number: 301-796-1231
Subject: NDA 21-247	

Total no. of pages including cover:

3

Comments: CMC Agreements

Document to be mailed: YES NO

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NDA 21-247

Dear Mr. Olchaskey:

We are reviewing your NDA application for Aerospan (flunisolide HFA, 80 mcg) Inhalation Aerosol, and we ask that you provide your agreements to the following requests by close of business on January 25, 2006.

1. Submit the test results for all flunisolide hemihydrate containers stored in the _____ facility in _____ as correspondence to the NDA.
2. Perform acceptance testing of drug substance batches no more than 90 days prior to its use in the formulation.
3. Reevaluate the _____ levels and revise the acceptance criteria based upon the results obtained from analysis of the first three post-approval production-scale batches. Submit a prior approval supplement for this change.
4. Adopt the proposed acceptance criteria for related substances in the drug substance on an interim basis until the _____ site is approved for use in this application. You will file a post-approval supplement to support the use of the new drug substance from the _____ site prior to its use in the manufacturing of the drug product (provided that _____ also submits a new DMF for the drug substance). For the flunisolide hemihydrate from _____ you will amend the NDA to include revised acceptance specifications wherein you commit to adopt the _____ specifications. After you have manufactured three full-scale batches at the _____ site, You and _____ must submit test results for review and reevaluation of the acceptance criteria.
5. Repeat the tests provided by _____ the Certificate of Compliance for the first three lots intended for commercialization. Thereafter, you agree to test every _____ lot manufactured by _____ annually. In addition, you agree to testing the first three commercial lots for extractables using Forest test procedure _____ and for product performance measured by _____), and medication delivery/through life (test methods _____).
6. Review the fill weight data with 3M after one year of production and revise these specifications if appropriate.

NDA 21-247

7. Reference is made to the November 20, 2002, meeting, in which you agreed to institute changes in your manufacturing process to minimize oxidation of flunisolide hemihydrate drug substance. Provide your agreement that you will follow up with this request.

8. Provide a _____
_____ actuation indicator.

I can be reached at 301-796-1231 for any questions.



Ladan Jafari, Regulatory Health Project Manager

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NDA 21-247

Drafted by: LJ/1-24-06

Initialed by: Barnes/1-24-06
Rogers/1-24-06
Peri/1-24-06
Lostritto

Filename: N21247agreements

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
1/25/2006 10:59:47 AM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 20, 2006

To: Michael Olchskey	From: Sandy Barnes for Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Products
Fax number: 201-524-9711	Fax number: 301-796-9718
Phone number: 201-386-2142	Phone number: 301-796-1174
Subject: NDA 21-247	

Total no. of pages including cover: 31

Comments: Labeling Comments

Document to be mailed: YES NO X

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Below are our additional preliminary comments regarding the labeling submitted on January 17, 2006, to your application for Aerospan HFA, NDA 21-247. Please submit draft labeling reflecting the revisions show below and in the attached labeling as soon as possible.

1. We have completed review of your proposed proprietary and established names. We have determined that the correct representation of these names are: AEROSPAN 80 mcg (flunisolide HFA 80 mcg) Inhalation Aerosol. Please revise all labeling to match this representation.
2. Add figures to represent the outcomes of the two studies in the Clinical Trials section.
3. Please re-check the numbers in the ADVERSE REACTIONS, PRECAUTIONS: Pediatric Use, and PRECAUTIONS: Geriatric Use sections. The numbers in the ADVERSE REACTIONS section should represent the number of patients exposed to AEROSPAN Inhalation Aerosol and placebo, but not flunisolide CFC inhalation aerosol. The numbers in the PRECAUTIONS: Pediatric Use and PRECAUTIONS: Geriatric Use sections should represent the number of patients exposed to AEROSPAN Inhalation Aerosol only.

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29 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sandra Barnes
1/20/2006 05:48:30 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 6, 06

To: Michael Olchaskey	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Products
Fax number: 201-524-9711	Fax number: 301-796-1231
Phone number: 201-386-2142	Phone number: 301-796-9728

Subject: Labeling for Aerospan

**Total no. of pages including
cover:** 45

Comments: Labeling comments

Document to be mailed: YES NO

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Below are our preliminary comments regarding the labeling submitted on July 27, 2005, and the container/carton labeling submitted on September 27, 2005, to your application for Aerospan HFA, NDA 21-247. Please let us know if you wish to discuss these comments in the teleconference scheduled for January 9, 2006, or to reschedule this teleconference to another time.

We have reviewed and revised all labeling, and recommend substantial changes. Note that we have asked you to supply new data points, figures, or new information in several locations within the product label. These areas are highlighted in yellow in the accompanying Word document. Our comments within the document are also highlighted.

1. We remind you that we have not yet agreed to your proposed storage conditions that appear in all labeling.
2. The following comments pertain to the proprietary and established names of your drug product.
 - a. Follow labeling requirements outlined in 21 CFR 201.10(g)(2), 21 CFR 201.15(a)(5), and 21 CFR 201.15(a)(6) for all instances of appearance of the proprietary name and established name on the container, carton, actuator, Package Insert (PI), and Patient Package Insert (PPI) of your drug product. In particular, we refer to the following:
 - i. All instances of the established name should be at least half the font size of the proprietary name. The font should be easily readable.
 - ii. Remove the "swoosh" from above the proprietary name Aerospan HFA, as it distracts from the proprietary name
 - b. You may wish to consider capitalization of your proprietary name throughout PI and PPI.
 - c. **While the suffix 'HFA' in your proprietary name is acceptable at this time, you should be aware that this is an interim acceptance of this suffix. The Agency has made the determination that at some time in the future this suffix, which has been appended to many of the HFA-propelled inhalational aerosol drug products, may be removed from all inhalational drug products bearing this term. This will occur at some time in the future after all CFC inhalational drug products are no longer available. At that time, we will ask all manufacturers of drug products with the suffix HFA to remove the term 'HFA' from their proprietary and established names, as this terminology will no longer be necessary.**

3. The following comments pertain to the labeling imprinted on the gray actuator.
 - a. Samples that you sent show the proprietary and established names imprinted on the gray spacer as Aerospan™ (flunisolide HFA) Inhalation Aerosol. This is not your current proprietary or established name. Please correct this.
 - b. Remove the "swoosh" from above the proprietary name Aerospan HFA.
 - c. Increase the font size of the established name.
4. The following comments pertain to the carton labeling.
 - a. Remove the "swoosh" from over the proprietary name Aerospan HFA.
 - b. Change the font for the established name to a font that is not a narrow font.
 - c. Display the route of administration "For Oral Inhalation Only" prominently and clearly on the principal display panel.
 - d. Display the product strength/actuation prominently on the principal display panel in conjunction with the proprietary name.
 - e. Increase the font size of the statements "60 metered actuations" and "120 metered actuations" and relocate them to follow the strength on the principal display panel.
 - f. **Revise the following statement on the principal display panel: "Canister to be used with Aerospan HFA inhalation aerosol actuator only." Include a statement that the actuator/spacer should be used only with the Aerospan HFA canister. Change the font to a less narrow font that is more readable.**
 - g. Revise the Usual Dose to remove the usual dose range, which is an inappropriate for adults and adolescents aged 12 years and older. Refer only to the Package Insert for dosage information.
5. The following comments pertain to the container labeling.
 - a. Our same comments for the carton labeling above apply to the container labeling.

- b. For the 5.1g package, increase the prominence of the statement **“PROFESSIONAL SAMPLE – NOT FOR RESALE”**.
6. The following comments pertain to the Package Insert.
- a. The DESCRIPTION and HOW SUPPLIED sections were extensively edited. The wording in these sections was updated to closely approximate analogous sections of other recently approved inhalational drug product labels.
 - b. The following comments pertain to the CLINICAL PHARMACOLOGY section.
 - i. This section was updated to match current labeling recommendations for inhalational corticosteroid drug products. Several subsections were added, including a Mechanism of Action and a Pharmacokinetics subsection.
 - ii. The Pharmacodynamics subsection was rewritten to more clearly present your PK/PD studies and the HPA axis data from the four clinical studies. Except for a general statement, specific HPA axis data from the previous CFC formulation was removed.
 - (1) In the first paragraph, add the C_{max} and AUC values for flunisolide and 6β-OH flunisolide from study ANC-PK-97-03 in the location marked after the description of the study. Show the results for the following dosage arms: flunisolide CFC 1000 µg and Aerospan HFA 320 µg.
 - (2) In the first paragraph, add the C_{max} and AUC values for flunisolide and 6β-OH flunisolide from study ANC-PK-97-04 in the location marked after the description of the study. Show the results for the following dosage arms: flunisolide CFC 1000 µg and Aerospan HFA 320 µg with spacer.
 - (3) In the last paragraph, we suggest that you also consider adding unstimulated cortisol measurements, if available, from the adult 12-week placebo-controlled study.
 - c. The CLINICAL TRIALS section was extensively edited to reflect the nature of the two pivotal trials. The following comments pertain to this section.
 - i. An introductory paragraph was added describing the study design for the two pivotal trials.

- ii. The subheading for the Adult and Adolescent Patients clinical trial should include the words "with Asthma."
 - iii. The clinical trial descriptions were extensively edited to more clearly reflect the outcome measures.
 - iv. Please check the oldest age of patients in ITT population for study AND-MD-01 in the appropriate locations in the first and second paragraphs.
 - v. Replace Figures 1 and 2 with figures that show the primary endpoint of change from **baseline** in percent predicted FEV₁. The figures shown reflect change from screening in percent predicted FEV₁. This was not the primary efficacy measure. Results should be represented with time on the X axis, and percent predicted FEV₁ on the Y axis. It would be useful to show the pre-baseline entry FEV₁ measure as well as baseline and all time points over the course of the study, while still representing the primary endpoint for each dosage on the right-hand side. Placebo and CFC treatment groups should be shown. In Figure 1, only the 160 and 320 mcg HFA dosages (not the 80 mcg), 500 and 1000 mcg CFC dosages (not the 250 mcg), and placebo should be represented. The legend should include the N for each dosage. The legend and text should use the same text to refer to the flunisolide CFC drug product. Place an asterisk next to any primary efficacy endpoint to denote that is statistically significant. A footnote should describe the primary endpoint and comparison. Figure 2 should follow a similar approach.
 - vi. Growth data was removed (see comments below).
 - vii. Statements regarding efficacy results from your long-term non-placebo-controlled safety studies were removed.
 - viii. Please ensure that the presentation of the pediatric study reflects the number of patients without site 26. Update the number of patients studied (as shown in the highlighted areas of the text).
- d. We have updated the WARNINGS and PRECAUTIONS sections of the label to match current labeling recommendations for inhalational corticosteroid drug products. The following comments pertain to the PRECAUTIONS section.

- i. We have removed the results of growth investigations in the pediatric safety study and from a growth study with Aerospan HFA from the Pediatric Use sub-section (and also from the Clinical Trials subsection). Growth data from the original NDA clinical trials was considered not interpretable. Results of the stand-alone growth study were included in the fourth cycle submission, but not reviewed. The study report for the growth study should be submitted as a supplement post-approval.
 - ii. The Geriatric Use subsection was updated with the latest recommended geriatric wording, based on the Geriatric Labeling Guidance. Please add the number and ages of patients studied in the geriatric age range.
- e. The following comments pertain to the ADVERSE REACTIONS section.
- i. This section was extensively edited. In particular, we have edited the first two paragraphs to more accurately reflect results of the two pivotal placebo-controlled studies.
 - ii. We have inserted what we believe to be the correct number of patients studied. Please ensure that these numbers are correct.
 - iii. Updated the number of patients and various subpopulations studied (as shown in the highlighted areas of the text).
 - iv. The primary AE table is acceptable.
 - v. We have more clearly delineated the paragraphs that describe Adverse Events from the non-placebo-controlled trials and from those reported for your previous CFC-propelled formulation.
- f. Wording and numbers in the OVERDOSAGE section were edited.
- g. The following comments pertain to the DOSING AND ADMINISTRATION section.
- i. The time to onset of symptom relief was not studied in the clinical trials with the HFA formulation. Therefore, more generic wording was substituted.

- ii. The proposed table to convert patients from the CFC to the HFA drug product in the DOSING AND ADMINISTRATION section is not acceptable. The proposed dosing schema was not evaluated; equivalence was not evaluated between the proposed doses of the HFA drug product and doses of the CFC drug product. Labeling in this section was modified to make it more generic to a range of doses that are clinically applicable to the individual patient.
- iii. Since patients maintained on oral corticosteroids were not studied during the HFA development program, the labeling should state as such and derive recommendations that are general to all patients being weaned from oral corticosteroids. We have modified this section accordingly.

7. The following comments pertain to the Patient Package Insert.

- a. Risk information should be presented separately from patient instructions for use. We have therefore separated the PPI into two sections, a 'Patient Information' section and an 'Instructions for Use' section. While the Patient Information section currently precedes the Instructions for Use section, both should be easy for patients to find. Consider how these two sections are presented so that risk information and instructions for use are both easily accessed by patients.
- b. The PPI was extensively edited to present information at the level of understanding of the patient, not the physician. For clarity, we have changed all text that is presented in a capital bolded font to a non-capital bolded font.
- c. Many of the figures will need to be replaced by updated figures. See highlighted comments within the document.
- d. We do not agree with your proposed description of the methodology for holding and actuating the device. The optimal position for activating this device is with the base of the device cradled at the base of the thumb, the hand at the side of the device, and the finger on top. This method for holding and actuating: 1) assures a more secure connection/orientation between the spacer and the actuator than with the currently recommended method; 2) is a more easily adopted geometry for the arm and wrist; and 3) is a more secure method of holding the device to lower the risk of dropping it during use. Revise text to describe this, and all figures to visually show this.

38 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Ladan Jafari
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 27, 2005

TO: Badrul Chowdhury, MD, Director
Division of Pulmonary and Allergy Products
HFD-570

VIA: Ladan Jafar, Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
HFD-570

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza Hepp, PharmD, Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCs Review of "Patient's Instructions for Use" for Aerospan HFA (flunisolide inhalation aerosol), NDA 21-247

The sponsor submitted product labeling (PI), which includes "*Patient's Instructions for Use*," for Aerospan HFA (flunisolide inhalation aerosol), NDA 21-247 on September 27, 2005.

Comments and Recommendations

1. The labeling submitted as *Patient's Instructions for Use* includes risk information that is related to the drug rather than the inhaler. However, *Patient's Instructions for Use* should be the procedural steps to follow in setting up, using, cleaning, and storing the inhaler. It is the "how to" for the inhaler. We deleted the information on disease management and risks that are not specific to the inhaler.
2. We developed a Patient Package Insert (PPI) for consideration. The PPI includes comprehensive risk information for patients to accompany the patient's *Instructions for Use*. Patients should not have to refer to the PI for risk information. The PI is written for healthcare professionals and is not easily understood by most patients.
3. Never use all uppercase letters to emphasize a statement. All uppercase letters are difficult to read. Use a mix of upper and lowercase letters and emphasize the statement by bolding or increasing the font size.

75 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

ORIG AMENDME

N-000 BL



FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

DUPLICATE

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DEC - 8 2005

CDR / CDER

Direct Line: (201) 386-2142

Fax: (201) 524-9711

December 7, 2005

Badrul Chowdhury, MD, PhD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

DEC 09 2005

CDER White Oak DR1

NDA: 21-247 Aerospan HFA (flunisolide inhalation aerosol)
Re: Response to Request for Information: Carton and Container Labels

Dear Dr. Chowdhury:

Reference is made to the telephone request from Ms. Ladan Jafari for additional copies of the carton and canister labels.

Enclosed, please find 5 copies of each canister and carton labels for the trade size, _____ and _____

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Doreen V. Morgan at (201) 386-2131.

Sincerely,

Michael K. Olchaskey, PharmD
Associate Director, Regulatory Affairs
michael.olchaskey@frx.com

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; Mail Stop 4447)**

DATE RECEIVED: October 20, 2005	DESIRED COMPLETION DATE: December 27, 2005	ODS CONSULT #: 01-0050-4
DATE OF DOCUMENT: September 27, 2005	PDUFA DATE: January 27, 2006	

TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products
HFD-570

THROUGH: Ladan Jafari
Project Manager
HFD-570

PRODUCT NAME:
Aerospan HFA
(Flunisolide Inhalation Aerosol)
80 mcg of flunisolide hemihydrate per actuation

NDA SPONSOR: Forest Pharmaceuticals, Inc.

NDA#: 21-247

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Aerospan HFA, provided that only one name Aerospan HFA (NDA 21-247) or _____ is approved. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Aerospan HFA, acceptable from a promotional perspective.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 796-2360 Fax: (301) 796-9865

exceed 4 inhalations twice daily. The recommended initial dose for children (age 6 to 11) is one inhalation twice daily (morning and evening), not to exceed a maximum dose of 2 inhalations twice daily. Higher doses in children have not been studied. Aerospan HFA is supplied as a pressurized aluminum canister with a two piece purple actuator/gray spacer assembly in one box. Each actuation delivers approximately 80 mcg flunisolide hemihydrate (equivalent to 78 mcg flunisolide) to the patient. Aerospan HFA will be available in an 8.9 gram (containing 120 inhalations) and a 5.1 gram (containing 60 inhalations) net weight canister.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Aerospan HFA to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Aerospan HFA. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Aerospan HFA, acceptable from a promotional perspective.
2. The Expert Panel identified one additional proprietary name that was thought to have potential for confusion with Aerospan HFA. This product is listed in table 1 (see page 4), along with the dosage form and usual dosage.

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2005, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

⁴ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

Aerospan HFA and Aerospyr are approved by the Agency, as the two have overlapping product and look-alike characteristics. Aerospan and _____ each have six identical beginning letters (“Aerosp”) and end with a similar looking letter (“n” vs. “-”) when scripted. _____ has one additional downstroke letter “-” towards the end of the name, but this may be easily overlooked as the beginning of each name is identical. Besides look-alike similarities, the two drugs have overlapping directions for use (2 inhalations BID vs. 2 mL BID), frequency of administration (twice daily), route of administration (oral inhalation/nebulization), and patient/prescriber population. In addition, _____ is indicated for the treatment of bronchoconstriction in patients with COPD and Aerospan is NOT indicated for the relief of acute bronchospasm. This difference in indication for use may be of safety concern if one drug is inadvertently administered instead of the other. DMETS has no objections to the use of the proposed proprietary name Aerospan HFA provided that only one name, Aerospan HFA (NDA 21-247) or _____ is approved.

Aerospan _____

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the re-review of the container labels, carton and insert labeling of Aerospan HFA, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS provided suggestions for improvement on the labels and labeling in the last review. Many of the label and labeling comments provided in this review were included in ODS Consult 01-0050-3 dated March 31, 2004, but were not incorporated in the revised labels and labeling. Additionally, DMETS has identified several additional areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

DMETS notes the use of trailing zeroes throughout the package insert labeling. For example, the Pharmacodynamics section of the CLINICAL PHARMACOLOGY section states, “Administration of flunisolide hemihydrate 2.0 mg twice daily....” The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, “...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero.” In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labeling so that strengths, etc. are expressed without the use of a terminal zero (e.g., the dosage should read 2 mg instead of 2.0 mg).

B. CONTAINER LABELS

1. The product strength/actuation should be prominently placed on the principal display panel in conjunction with the proprietary name. Additionally, the statements “60 metered actuations” and “120 metered actuations” should be relocated to follow the strength on the principal display panel. For example, “The dose delivered per actuation from the mouthpiece is 80 mcg flunisolide hemihydrate. Contains 60 actuations per canister.”

- c. In the table, the dose conversion is expressed in concentration (mcg) of the inhalation. In addition to the mcg, a column for number of inhalations per dose should be included to minimize the risk of potential miscalculation of number of inhalations to be used per dose.
- d. The paragraph following the table describes clinical trials performed in children ages 4-11 who successfully transferred from flunisolide CFC to flunisolide HFA. Since Aerospan HFA is indicated to treat children older than 6 years of age, this contradicts the recommended age group of children and may cause confusion. Please comment.

3. PATIENT'S INSTRUCTION FOR USE

- a. The first paragraph of the DIRECTIONS for USE section currently reads, "Before using new AEROSPAN HFA...." Revise line 679 to read, "Before using a new AEROSPAN HFA...." to avoid misunderstanding of the word "new".
- b. The third paragraph of the DIRECTIONS for USE section is numbered and the fourth bullet reads, "Check that the canister is fully seated in the actuator." To enhance clarity, please revise the sentence to read as follows, "Check that the canister is completely inserted into the actuator."
- c. Clarify the picture in Figure 1 by labeling the canister, mouthpiece and actuator.
- d. Bold the statement in Step 5 – Using Your Aerospan HFA which reads, "If you are using the inhaler for the first time, or if the inhaler has not been used for more than 2 weeks, you will need to prime (prepare) the inhaler" to ensure patients are aware of this important information.
- e. In Figure 11, delete the downward arrow shown. It indicates depressing the actuator, when the figure and narrative demonstrates placing the actuator in the mouth.

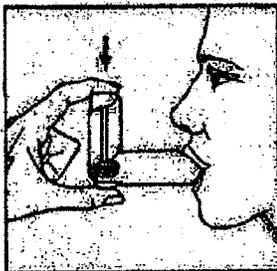


Figure 11

- f. Bold and highlight the word "Caution" in the warning statement following Step 10.
- g. In Figure 12, add a downward arrow to accentuate depressing the actuator.

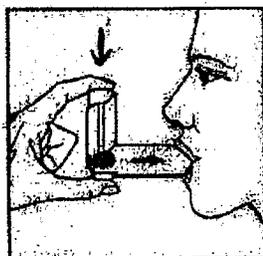


Figure 12

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11/10/2005 03:42:13 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/10/2005 04:16:04 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/14/2005 12:52:10 PM
DRUG SAFETY OFFICE REVIEWER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-247

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: Michael K Olchaskey, Pharm.D.
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

We acknowledge receipt on July 27, 2005 of your July 26, 2005, resubmission to your new drug application for Aerospan HFA (flunisolide inhalation aerosol).

We consider this a complete, class 2 response to our April 20, 2004, action letter. Therefore, the user fee goal date is January 27, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the pediatric study requirement for ages 0 months to less than 6 months. We are also deferring submission of your pediatric studies for ages 6 months to less than 6 years until August 12, 2008. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

NDA 21-247

Page 2

If you have any question, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

(See appended electronic signature page)

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary & Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
8/29/2005 02:38:03 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: August 25, 2004

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084
Subject: NDA 21-247	

Total no. of pages including cover: 3

Comments: August 4, 04 Meeting Minutes

Document to be mailed: YES NO

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NDA 21-247

Drug: Aerospan (flunisolide HFA inhalation aerosol)

Date of Telecon: August 4, 2004

IMTS: 13612

Page 1

Forest Representatives:

Robert Ashworth, Ph.D., Senior Director, Regulatory Affairs

David Lust, Acting Director, Regulatory Affairs

Sebastian Assenza, Ph.D., Vice President, Process Research & Development

Shashank Mahashabde, Ph.D., Vice President, Formulation Development

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Brian Rogers, Ph.D., CMC Reviewer

Richard Lostritto, Ph.D., CMC Team Leader

Ladan Jafari, Regulatory Project Manager

Background: Forest submitted a request for a teleconference dated July 6, 2004, to discuss the container closure system for Aerospan. The current container closure system for Aerospan consists of _____ aluminum canister. Forest proposed to change the _____ canisters to _____ canisters. To ensure that drug will not degrade due to exposure to a larger surface area of _____ from the canister, Forest proposed to conduct a comparability study, and manufacture _____ scale pilot batches in support of the change to the _____ canister. Forest asked if the Division would agree with the proposed plan.

Discussions:

The Division asked Forest about the material of composition of the other components of the container closure system. Forest responded that _____ is used for all valve components as well. However, the _____ made of aluminum. 3M would manufacture the new canisters for Forest. The Division asked about the development plans for _____ Forest responded that the manufacturing process is : _____

The Division responded that in general we agree with the concept of changing to a _____ canister, but we have additional concerns. These concerns are outlined below:

- Since the manufacturing process for the valve and the canister are different, we expect different surface characteristics, both physical and chemical in nature, especially since the canisters will be _____. The Division also indicated that although the same alloy is used, the surface area is significantly different and there will be _____ present in the canister since it will _____
- The acceptability of the change is a review issue.

NDA 21-247

Drug: Aerospan (flunisolide HFA inhalation aerosol)

Date of Telecon: August 4, 2004

IMTS: 13612

Page2

- Submit the 6-month stability data during the first 3 months of the review cycle.
- Submit comparative data from production on stress-tested and aged samples of both new and old canister product. These data will also be needed for the batches manufactured post-approval to justify extension of the expiry. Submitted data should include frequency of failure for weight-check and valve function.
- Examine the new canisters in the stability study at all time points specifically for corrosion and gasket damage at the canister/gasket interface using optical microscopy. Forest indicated that they would examine approximately _____ canisters for failure. The Division stated that Forest should also evaluate the crimp height to assure that the canisters are sealed properly. The Division asked that Forest provide data on the relative frequency of failure data for both leakage and valve function after lagging. This investigation should be done both after the laboratory-scale manufacturing run and post-approval as a Phase 4 commitment on the first full-scale production batch.
- Test for extractables and propose updated acceptance criteria for all extractives including _____
- Reevaluate both the acceptance criteria for foreign particulates and the need for canister cleaning based on the presence of foreign particulates of possibly new types and sizes and canister residues.

Forest also asked that if no stability issues are observed, does the Division agree that the product in _____ canisters can be approved with a shelf-life of 24 months based on the stability data submitted with the _____ canisters.

- The Division did not agree, and stated that the initial expiry granted is a review issue. Extension of the initially-approved expiry will be based on data evaluation of the production-scale batches manufactured post-approval.
- Forest should submit a prior-approval supplement to extend the expiry with appropriate stability data to support the proposed extension after approval, and submit data on leachables levels at every time point in the long-term and accelerated stability studies once a validated analytical method for leachables has been developed for the _____

Forest asked if the Division had any comments in case Forest decides to use _____ canisters. The Division did not have extensive comments at this time but reminded Forest that the issues to support the use of _____ canisters will be similar to those already submitted to support the use of _____ canisters.

Action: The Division reminded Forest that the comments provided here are not all inclusive and there may be more comments once additional data are provided and reviewed. Forest indicated that they would consider the Division's comments internally before they respond to the approvable letter.

NDA 21-247

Drug: Aerospan (flunisolide HFA inhalation aerosol)

Date of Telecon: August 4, 2004

IMTS: 13612

Page3

Drafted by: LJ/8-9-04

Initialed by: Rogers/8-9-04
Lostritto/8-24-04

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/s/

Ladan Jafari
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 21, 2004

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084

Subject: NDA 21-247

Total no. of pages including cover: 3

Comments: CMC Tcon minutes

Document to be mailed: YES NO

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NDA 21-247
Drug: Aerospan
Applicant: Forest
Telecon Date: May 13, 2004

Forest Representatives:

David Lust, Associate Director, Regulatory Affairs
Sebastian Assenza, Ph.D., Analytical Research
Shashank Mahashabde, Ph.D., Director, Formulations Development

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Brian Rogers, Ph.D., CMC Reviewer
Richard Lostritto, Ph.D., CMC Team Leader
Ladan Jafari, Regulatory Project Manager

Background: Forest submitted a general correspondence dated May 3, 2004, and asked for clarification on two of the deficiencies cited in the approvable letter dated April 20, 2004. The deficiencies of the Agency letter are printed in *Italics* below followed by the discussions.

1. *As stated in our letter dated July 30, 2003, modify all labeling to indicate that the recommended storage conditions are —25°C. Since the drug product is a solution formulation with only a — margin for error to prevent precipitation at 15°C, and the real-life storage conditions may exceed the labeled recommendations by a significant margin, the narrowest possible range should be specified on the labels to alert shippers and patients of the need for careful storage (Comment 17.a).*
- Forest indicated that based on their data on temperature cycling between -10°C and 40°C over a six week period and the time required to obtain a solution formulation after cooling the canisters of drug product to -20°C, precipitation of the drug substance was not an issue. Forest further discussed normal storage conditions and indicated that warehouses may not maintain the required storage conditions, therefore, requested that storage conditions be modified to —25°C with excursions permitted between 15-30°C.
 - The Division stated that an excursion statement cannot be permitted, and explained that dose uniformity would be lost if the solution becomes a suspension. The Division also explained that at this point Forest's target formulation composition allows for a — drug substance overfill at 15°C to maintain a solution formulation. This means that if the drug substance is overfilled or the formulation solvent underfilled by more than this percentage, the formulation will no longer be a solution. The Division noted that this percentage of overfill will still permit passing mean emitted-dose acceptance criteria as long as the formulation remains a solution. The Division indicated that Forest designed their cycling study with a target fill weight and was not a worst-case scenario. The Division

NDA 21-247

Drug: Aerospan

Applicant: Forest

Telecon Date: May 13, 2004

Page 2

is concerned that if the formulation becomes a suspension over a long period of time or under unforeseen conditions, it may not become a solution again before use or may not be a uniform solution after reconstitution of the suspension. Forest has not provided any data on dose uniformity with a suspension formulation or a reconstituted solution formulation (one that has become a suspension and the precipitate redissolved without shaking).

- The Division stated that if Forest wants to insert a wider storage conditions statement in the labeling, they must design a study to address the above issues. An example of such a study design should include a worst case scenario, possibly using a glass bottle and visually inspect the formulation over a six-month time span. Since the Aerospan formulation includes ethanol _____, this experiment should at least be performed with a low fill weight of ethanol, low and high propellant fill weights, and high drug substance overfill. The Division indicated that it is amenable to discuss proposals for study designs to address this issue.

2. *Revise the established name and proprietary name to Aerospan HFA (flunisolide inhalation aerosol). The name Aerospan is associated with the delivery system, therefore, inhalation aerosol should appear within the parenthesis as part of the established name. HFA is not part of the established name, therefore, it should not appear in the parenthesis as part of the established name.*

- The Division asked that Forest clarify the name Aerospan as it was submitted for trademark application.
- Forest indicated that Aerospan was incorrectly submitted to the trademark office as including an empty canister. Forest is in the process of correcting this error. Forest indicated that they will follow up with this issue once the trademark application is corrected.

Action: Forest will internally discuss the design of a study to address labeling with regard to storage conditions, and will inform the Division as to how they wish to address this issue. Forest will also inform the Division of the contents of the trademark application once it is corrected by Forest and accepted by the appropriate Agency.

NDA 21-247
Drug: Aerospan
Applicant: Forest
Telecon Date: May 13, 2004
Page 3

Drafted by: LJ/5-19-04

Initialed by: Rogers/5-20-04
Lostritto/5-20-04

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-247

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: David A. Lust
Acting Director, Regulatory Affairs

Dear Mr. Lust:

Please refer to your new drug application (NDA) dated April 27, 2000, received April 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aerospan HFA (flunisolide inhalation aerosol).

We acknowledge receipt of your submissions dated August 20, October 20, and December 12, 17, and 19, 2003, and January 12, and 14, and March 31, 2004.

The October 20, 2003, submission constituted a complete response to our July 30, 2003, action letter. Clinical study submitted in the October 20, 2003, amendment has not been reviewed in this review cycle.

We completed our review of this application, as amended, and it is approvable. Before the application(s) may be approved, however, it will be necessary for you to address the following deficiencies. (Note that parenthesis following our comments refer to comments listed in the July 30, 2003, action letter.)

1. We agree with your proposal that the dose delivered from the mouthpiece be expressed as 80 mcg flunisolide hemihydrate per actuation (equivalent to 78 mcg flunisolide). Modify the labeling as appropriate (Comment 7).
2. DMF — remains inadequate to support your application. A letter was sent to the DMF holder (Comment 9).
3. All comments on leachables acceptance criteria are deferred until issues related to leachables levels are made adequate in DMF — (Comment 11).

4. Your approach to leachables testing with the associated footnote in the specification sheet and the Stability Protocol pertaining to extractables testing in lieu of leachables testing, may be acceptable. Consequently, your proposed approach to extractables/leachables testing may not be necessary. The acceptance criteria for leachables have not yet been agreed to. DMF _____ remains inadequate to support your application in this regard (Comments 14.a.-b.).

Submit revised draft labeling addressing the following deficiencies.

5. As stated in our letter dated July 30, 2003, modify all labeling to indicate that the recommended storage conditions are _____ 25°C. Since the drug product is a solution formulation with only a _____ margin for error to prevent precipitation at 15°C, and the real-life storage conditions may exceed the labeled recommendations by a significant margin, the narrowest possible range should be specified on the labels to alert shippers and patients of the need for careful storage (Comment 17.a.).
6. Revise the established name and proprietary name to Aerospan HFA (flunisolide inhalation aerosol). The name *Aerospan* is associated with the delivery system, therefore, inhalation aerosol should appear within the parenthesis as part of the established name. HFA is not part of the established name, therefore, it should not appear in the parenthesis as part of the established name.
7. Modify the prominence of the established name and/or proprietary name in all instances to make them equal. The established name appears significantly less prominent than the proprietary name in the submitted labeling. (Comment 17.c.).
8. As stated in our June 30, 2003, letter, modify the drug product carton to include the statement "*CANISTER IS TO BE USED WITH AEROSPAN HFA INHALATION AEROSOL ACTUATOR ONLY*". Your proposed wording implies that the carton contents are to be used only with the Aerospan actuator. This would be correct if the carton contained only a canister. Since the carton contains both the actuator/spacer and the canister, a more accurate statement is necessary (Comment 19.a.).
9. As requested in our letter dated July 30, 2003, delete the paragraph that pertains to the radiolabeled deposition study. This was moved to the CLINICAL PHARMACOLOGY section of the Package Insert (Comment 20.a.4.).
10. The units in all labeling should be separated from the value of the data by a space (e.g., 61 mcg instead of 61mcg, and 40 L/min instead of 40L/min). Please note that your corrections within the body of the amendment are in accordance with this request (Comment 20.b.1.).
11. Reinstigate the description of the _____ in the HOW SUPPLIED section along with NDC number as requested in a previous comment.
12. Remove all references to clinical study AMC-MD-07 from the package insert.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.509d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

In addition to the above deficiencies, we have the following comments.

13. As stated in our June 30, 2003, letter, insert the NDC code on the professional sample labeling where applicable since the NDC code is critical as a unique product identifier, and is useful for rapid determination of identity and communication between pharmacies and laboratories (Comment 17.f.).
14. Provide the status and a proposed timeline for introduction of the actuation counter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendments, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division/ the Division of Pulmonary & Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
4/20/04 04:13:39 PM

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: December 18, 03

To: David Lust	From: Ladan Jafari
Company: Forest	Division of Pulmonary and Allergy Drug Products
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1084
Subject: NDA 21-247	

Total no. of pages including cover: 2

Comments: CMC information request

Document to be mailed: YES NO

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We are reviewing your NDA submission and have the following requests for information. We would appreciate an expedited response to these requests.

1. Clarify how the technique for expending waste actuations in the previous version of the through-life/medication delivery assay test method differed from that used to waste actuations in the method for determining particle size distribution by where there was a significantly weaker trend from beginning- to end-of- canister in the determination (Comment 6 of the approvable letter dated July 30, 2003).
2. Clarify how drug deposited on the canister may affect the through-life medication delivery in the manner seen in the original data (Comment 6 of the approvable letter dated July 30, 2003).
3. Provide the data in Attachment 9 in tabular format with individual results listed. This is necessary for trend analysis (Comment 6 of the approvable letter dated July 30, 2003).
4. As requested in our letter dated July 30, 2003, provide an updated stability protocol containing all changes adopted in response to Comments 21.b-e in our letter dated May 8, 2003. Use of a separate "Post-Approval Stability Commitments" document is unacceptable.

I may be reached at 301-827-1084 for any questions concerning these requests.

Ladan Jafari, Regulatory Project Manager

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Page 2

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Rogers/12-18-03
Bertha/12-18-03

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ladan Jafari
12/18/03 09:13:58 AM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
HFD-570/DPADP

FACSIMILE TRANSMITTAL SHEET

DATE: May, 2003

To: David Lust	From: Sandy Barnes Division of Pulmonary and Allergy Drug Products
Company: Forest Laboratories	
Fax number: 201-524-9711	Fax number: 301-827-1271
Phone number: 201-386-2024	Phone number: 301-827-1050

Subject: Official Minutes for September 25, 2003 telecon for NDA 21-247

Total no. of pages including cover: 3

Comments: These are the Official minutes of the meeting.

Document to be mailed: • YES NO

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