PROCESSES FOR MAKING LACTOSE UTILIZING PRE-CLASSIFICATION TECHNIQUES AND PHARMACEUTICAL FORMULATIONS FORMED THEREFROM

Field of the Invention

The invention generally relates to processes for making lactose and pharmaceutical formulations formed therefrom.

Background of the Invention

In the field of inhalation therapy, it is generally desirable to employ therapeutic molecules having a particle size (i.e., diameter) in the range of 1 to 10μm. Carrier molecules or excipients, such as lactose, for inhaled therapeutic preparations also include significantly larger diameter particles (e.g., 100 to 150μm) that typically do not penetrate into the upper respiratory tract to the same degree as the active ingredient. In general, it is preferable to use a smaller particle size for the lactose or a lactose blend having a defined ratio of coarse and fine lactose.

The lactose particle size and distribution will also, in many instances, significantly influence pharmaceutical and biological properties, such as, for example, bioavailablity. For example, it is well known that coarse lactose in crystalline form has a fair flow rate and good physical stability whereas fine lactose powder, such as that produced by conventional fine grinding or milling, generally lacks good flow properties. Lactose prepared by conventional spray drying either lacks desired flow properties or contains too many large sized lactose crystals.

It is well known that one particular drawback associated with conventional means of producing pharmaceutical grade lactose relates to undesirable variations in particle size, morphology and distribution. Such production methods are particularly problematic in that they often lead to excessive and undesirable variations in the fine particle mass ("FPMass") of pharmaceutical formulations employing such lactose. FPMass is the weight of medicament within a given dose that reaches the desired size airways to be

effective. For example, a desired size may be defined as approximately 1 micron to 10 microns as measured by laser scattering techniques.

Lactose morphology is believed to be another important parameter to control, and it is believed that the degree of surface roughness can influence the interaction between the lactose particle and excipient and as such is now often measured as part of the lactose selection criteria. See e.g., Pharmaceutical Technology Europe April 2004, page 23.

It is possible that two lactose particles may be measured as having the same particle size, but if one is smooth, eg un-milled crystalline lactose, and the other is a rougher-surfaced milled crystal, that these could associate to a different extent with the active and thus impact upon either the initial FPMass performance or the through life stability performance of the product.

Summary of the Invention

The present invention attempts to address the above problems associated with conventional processes of producing lactose, and provides a process of producing lactose possessing reduced levels of variation for both particle size distribution and particle morphology.

In one aspect, the invention provides a process for forming lactose suitable for use in a pharmaceutical formulation and having a predetermined particle size distribution. The process comprises providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less; milling the plurality of lactose particles to yield a plurality of milled lactose particles with an average particle size, (D50), ranging from about 50 microns to about 100 microns; and then classifying the plurality of milled lactose particles into at least two fractions comprising a fine fraction and a coarse fraction wherein the fine fraction has an average particle size, (D50), ranging from about 3 microns to about 50 microns, and the coarse fraction has an average particle size, (D50), ranging from about 40 microns to about 250 microns. In one embodiment, appropriate amounts of coarse and fine fractions may be combined with at least one medicament to form a pharmaceutical formulation.

These and other aspects are encompassed by the present invention.

Brief Description of the Drawings

FIG. 1 illustrates a particle size profile for lactose formed in accordance with Example 1.

FIG. 2 illustrates a particle size profile for lactose formed in accordance with Example 2.

FIG. 3 illustrates a particle size profile for lactose formed in accordance with Example 3.

FIG. 4 illustrates a comparison of a particle size profile for lactose formed in accordance with Example 2 with two conventional production batches.

FIG. 5 illustrates the particles size distribution of the initial crystalline A feed lactose used in Examples 1, 2 and 3. This shows the varying amounts of lactose in the less than 60 micron region.

FIG. 6 illustrates the particles size distribution of the crystalline A feed lactose after it has been classified to remove the majority of the smaller crystalline lactose particles.

FIG. 7 illustrates the correlation between D10 and the Span of Feed Lactose Batches.

FIG. 8 illustrates the particle size distribution for pre-classified lactose, coarse fraction.

Detailed Description of the Invention

The invention will now be described with respect to the embodiments set forth herein. It should be appreciated that these embodiments are set forth to illustrate the invention, and that the invention is not limited to these embodiments.

All publications, patents, and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

It must be noted that, as used in the specification and appended claims, the singular forms "a", "an", "one" and "the" may include plural references unless the content clearly dictates otherwise.

As used herein, the term "D50" is defined as the size in microns above or below which 50 percent of the particles reside on a volume basis.

The process for forming lactose in accordance with the present invention may encompass various embodiments. For example, in one embodiment, the step of milling the plurality of lactose particles to yield a plurality of lactose particles may encompass obtaining those particles with an average particle size (D50) ranging from about 50, 55, 60, 65, 70 or 75 microns to about 70, 75, 80, 85, 90, 95 or 100 microns. In one embodiment, for example, the step of classifying the plurality of milled lactose particles into at least two fractions may result in a fine fraction having an average particle size (D50) ranging from about 3, 10, 15, 20, 25, 30 or 35 microns to about 30, 35, 40, 45 or 50 microns as well as a coarse fraction having an average particle size (D50) ranging from about 40, 75, 100, 125 or 150 microns to about 100, 125, 150, 175, 200, 225 or 250 microns, as measured by Malvern particle sizing.

In accordance with the present invention, the term "lactose" as used herein is to be broadly construed. As an example, lactose is intended to encompass physical, crystalline, amorphous and polymorphic forms of lactose, including, but not limited to, the stereoisomers α-lactose monohydrate and β-anhydrous lactose, as well as α-anhydrous lactose. Combinations of the above may be used.

Lactose (i.e., milk sugar) is preferably obtained from cheese whey, which can be manufactured in different forms depending on the process employed. As used herein, the term "particle" is to be broadly interpreted to encompass those of various shapes, sizes, and/or textures which can include those that may have varying degrees of irregularities, disuniformities, etc. or which may possess regular and/or uniform properties.

The plurality of lactose particles used in the process of the present invention may be acquired in various manners. In one embodiment, the plurality of lactose particles is present in the form of crystalline or unmilled lactose. In one embodiment, the initial step of providing lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less, comprises obtaining the plurality of lactose particles from a crystallization process. One example of a

suitable crystallization process that may be employed is set forth in copending U.S. Application entitled "Process for Crystallizing Lactose Particles for Use in Pharmaceutical Formulations", Serial No.60/651,754 filed concurrently herewith. It should be understood that other processes may also be employed.

In another embodiment, the initial step of providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less, comprises obtaining the plurality of lactose particles by sieving a source of lactose to produce the plurality of lactose particles. Typical examples of commercially available sieving apparatus are made available by Russell Finex of Charlotte, North Carolina and Alpine Sieves of Augsburg, Germany.

In another embodiment, the plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less may be obtained by classifying a source of lactose into two fractions comprising the plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less and a remaining fine fraction. One example of a commercially preferred classifier made commercially available by Hosakawa of Cheshire, United Kingdom. The remaining fine fraction of lactose is lactose that is unmilled or crystalline. Optionally, prior to classifying, the particles may be subjected to sieving.

FIG. 5 illustrates the full particle size profile of the initial feed batches before the smaller crystals have been removed by classification. **FIG. 6** illustrates the full particle size profile after the smaller crystals have been removed via a classification process. This results in a much more uniform feed material being presented to the mill.

The Span is often a parameter used to describe the narrowness / broadness of a distribution of particles. The Span is given by the following formulation:

$$(D90 - D10)/D50 = \text{Span}$$

The term "D90" is defined as the size in microns below which 90 percent of the particles reside on a volume basis.

The term "D10" is defined as the size in microns below which 10 percent of the particles reside on a volume basis.

Although not intending to be bound by theory, for particles with similar D50's the smaller the Span, the tighter are the distribution of particles. In general, feed lactose batches with small Span values would be better input materials to the mill as this would indicate a narrower particle size distribution. It can be seen from **FIG. 7** that the higher the D10 values are for typical crystalline A Feed lactose batches, the smaller the Span values. The following Tables 1-2 illustrate that tighter particle size distributions are obtained after the classification of the crystalline A Feed lactose, and hence produce a preferred input into the mill

Table 1

Malvern Data Prior to classification				
	D10	D50	D90	Span
Example 1 Fine feed	57	123	208	1.23
Example 1 coarse feed	86	176	284	1.13
Example 2 Fine feed	53	114	208	1.36
Example 2 coarse feed	84	162	270	1.15
Example 3 Fine feed	53	114	207	1.35
Example 3 coarse feed	81	161	274	1.20

Table 2

Malvern Data after classification				
	D10	D50	D90	Span
Example 1 Fine feed	88	141	219	0.93
Example 1 coarse feed	116	186	284	0.90
Example 2 Fine feed	79	140	236	1.12
Example 2 coarse feed	107	171	263	0.91
Example 3 Fine feed	81	139	230	1.07
Example 3 coarse feed	104	171	270	0.97

The step of milling the plurality of lactose particles to yield a plurality of milled lactose particles may be carried out using known techniques. As an example, in one embodiment, milling may be performed using an impact mill (e.g., air classifier mill, (ACM)) whereby size reduction of pharmaceutical grade lactose is a combination of milling and classification. In one

embodiment, milling is conducted using a standard air classifier mill fitted with mill rotor and grinding pins, classifier wheel and grinding track. One example of a commercially preferred mill is the MikroPul ACM made commercially available by Hosakawa.

The process described herein is suitable for providing lactose for use in a wide range of inhalation applications, encompassing those that require very fine lactose to those requiring much coarser lactose. Such that in one embodiment the coarse fraction alone may be suitable for pharmaceutical applications and at the other extreme the fine fraction alone may be suitable for pharmaceutical applications. Required FPMass performance from inhalation devices, including, in one embodiment and without limitation Advair, can be targeted by the combination of appropriate amounts of the coarse and fine fractions. This can cover the complete range from 100 percent coarse fraction + 0 percent fine fraction to 100 percent fine fraction + 0 percent coarse fraction. The exact proportions that are required will depend on the particle size profile of each of the coarse and fine fractions themselves.

As an example, the above combining step may be achieved by blending, although other procedures may be employed. A typical blender used would be of the orbital screw type such as the Vrieco-Nauta Conical Blender made commercially available by Hosakawa.

In another aspect, the invention may encompass pharmaceutical formulations formed according to various processes set forth herein.

Medicaments, for the purposes of the invention, include a variety of pharmaceutically active ingredients, such as, for example, those which are useful in inhalation therapy. In general, the term "medicament" is to be broadly construed and include, without limitation, actives, drugs and bioactive agents, as well as biopharmaceuticals. Various embodiments may include medicament present in micronized form. Appropriate medicaments may thus be selected from, for example, analgesics, (e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine); anginal preparations, (e.g., diltiazem); antiallergics, e.g., cromoglicate, ketotifen or nedocromil); antiinfectives (e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine); antihistamines, (e.g., methapyrilene); anti-inflammatories, (e.g., beclometasone dipropionate, fluticasone propionate, flunisolide, budesonide,

rofleponide, mometasone furoate, ciclesonide, triamcinolone acetonide, 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester), (6α,11β,16α,17β)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate, and (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 4-methyl-1,3-thiazole-5-carboxylate); antitussives, (e.g., noscapine); bronchodilators, e.g., albuterol (e.g. as sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g as hydrobromide), formoterol (e.g., as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g., as acetate), reproterol (e.g., as hydrochloride), rimiterol, terbutaline (e.g., as sulphate), isoetharine, tulobuterol,4-hydroxy-7-[2-[[2-[[3-(2-(henylethoxy)propyl]sulfonyl]ethyl]-amino]ethyl-2(3H)-benzothiazolone), 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino)hexyl]oxy}butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl] oxy}propyl) benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2-phenylethyl]amino} phenyl)ethyl]amino}ethyl)phenylformamide, 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino]phenyl}ethyl)amino]ethyl}quinolin-2(1*H*)-one,
5-[(*R*)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamnino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one
; diuretics, (e.g., amiloride, ; anticholinergics, e.g., ipratropium (e.g., as bromide), tiotropium, atropine or oxitropium); hormones, (e.g., cortisone, hydrocortisone or prednisolone); xanthines, (e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline); therapeutic proteins and peptides, (e.g., insulin). It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity

and/or stability of the medicament. It will be further clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example, R-salbutamol or RR-formoterol.

Particular medicaments for administration using pharmaceutical formulations in accordance with the invention include anti-allergics, bronchodilators, beta agonists (e.g., long-acting beta agonists), and anti-inflammatory steroids of use in the treatment of respiratory conditions as defined herein by inhalation therapy, for example cromoglicate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), bitolterol, formoterol (e.g. as the fumarate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclometasone ester (e.g. the dipropionate), a fluticasone ester (e.g. the propionate), a mometasone ester (e.g., the furoate), budesonide, dexamethasone, flunisolide, triamcinolone, tripredane, (22R)-6α,9α-difluoro-11β,21-dihydroxy-16α,17α -propylmethylenedioxy-4-pregnen-3,20-dione. Medicaments useful in erectile dysfunction treatment (e.g., PDE-V inhibitors such as vardenafil hydrochloride, along with alprostadil and sildenafil citrate) may also be employed. It should be understood that the medicaments that may be used in conjunction with the inhaler are not limited to those described herein.

Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof may be employed.

It will be appreciated by those skilled in the art that the formulations according to the invention may, if desired, contain a combination of two or more medicaments. Formulations containing two active ingredients are known for the treatment and/or prophylaxis of respiratory disorders such as asthma and COPD, and may include, for example, formoterol (e.g. as the fumarate) and budesonide, salmeterol (e.g. as the xinafoate salt) and fluticasone (e.g. as the propionate ester), salbutamol (e.g. as free base or sulphate salt) and beclometasone (as the dipropionate ester).

In one embodiment, a particular combination that may be employed is a combination of a beta agonist (e.g., a long-acting beta agonist) and an anti-inflammatory steroid. One embodiment encompasses a combination of

fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt). The ratio of salmeterol to fluticasone propionate in the formulations according to the present invention is preferably within the range 4:1 to 1:20. The two drugs may be administered in various manners, simultaneously, sequentially, or separately, in the same or different ratios. In various embodiments, each metered dose or actuation of the inhaler will typically contain from 25 µg to 100 µg of salmeterol and from 25 µg to 500 µg of fluticasone propionate. The pharmaceutical formulation may be administered as a formulation according to various occurrences per day. In one embodiment, the pharmaceutical formulation is administered twice daily.

Embodiments of specific medicament combinations that may be used in various pharmaceutical formulations are as follows:

1) fluticasone propionate 100 µg/ salmeterol xinafoate 72.5 µg (equivalent to salmeterol base 50 µg)

2) fluticasone propionate 250 µg/ salmeterol xinafoate 72.5 µg (equivalent to salmeterol base 50 µg)

3) fluticasone propionate 500 µg/salmeterol xinafoate 72.5 µg (equivalent to salmeterol base 50 µg)

In various embodiments, the pharmaceutical formulations may be present in the form of various inhalable formulations. In one embodiment, the pharmaceutical formulation is present in the form of a dry powder formulation, the formulation of such may be carried out according to known techniques. The invention also encompasses inhalation devices including inhalable formulations. Dry powder formulations for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminum foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base which includes lactose and, optionally, at least one additional excipient (e.g., carrier, diluent, etc.). In various embodiments, each capsule or cartridge may generally contain between 20 µg and 10 mg of the at least one medicament. In one embodiment, the formulation may be formed into

particles comprising at least one medicament, and excipient material(s), such as by co-precipitation or coating. When employed as a dry powder, packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (e.g., as in Diskus®, see GB 2242134/ U.S. Patent Nos. 6,032,666, 5,860,419, 5,873,360, 5,590,645, 6,378,519 and 6,536,427 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Pat. Nos. 4,778,054, 4,811,731, 5,035,237) or metered in use (e.g. as in Turbuhaler, see EP 69715, or in the devices described in U.S. Patent No 6,321,747). An example of a unit-dose device is Rotahaler (see GB 2064336). In one embodiment, the Diskus® inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing the at least one medicament, the lactose, optionally with other excipients. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the base sheet.

In one embodiment, the formulations may be employed in or as suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Such formulations may be delivered via a pressurized inhaler, e.g., a Metered Dose Inhaler (MDI). Exemplary MDIs typically include canisters suitable for delivering the pharmaceutical formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminum can which may optionally be anodised, lacquer-coated and/or

plastic-coated, which container is closed with a metering valve. Aluminum cans which have their inner surfaces coated with a fluorocarbon polymer are particularly preferred. Such polymers can be made of multiples of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (EFTE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Embodiments of coatings used on all or part of the internal surfaces of an MDI are set forth in U.S. Patent Nos. 6,143,277; 6,511,653; 6,253,762; 6,532,955; and 6,546,928.

MDIs may also include metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK356) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser^{TM}). Embodiments of metering valves are set forth in U.S. Patent Nos. 6,170,717; 6,315,173; and 6,318,603.

In various embodiments, the MDIs may also be used in conjunction with other structures such as, without limitation, overwrap packages for storing and containing the MDIs, including those described in U.S. Patent No. 6,390,291, as well as dose counter units such as, but not limited to, those described in U.S. Patent Nos. 6,360,739 and 6,431,168.

In addition to the above, the pharmaceutical formulations can be employed in capsules, sachets, tablet buccals, lozenges, papers, or other container. Moreover, the formulations can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, capsules (such as, for example, soft and hard gelatin capsules), suppositories, sterile injectable solutions, and sterile packaged powders. Excipients, carriers, diluents, and the like may be optionally employed.

The pharmaceutical formulation formed by the processes of the invention may be used in the treatment of a number of respiratory disorders,

which encompasses, for example, maintenance treatment and/or prophylaxis. Such respiratory conditions include, without limitation, diseases and conditions associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, such as allergic and seasonal rhinitis). Such treatment is carried out by delivering medicament to a mammal. Accordingly, and in view of the above, in another aspect, the invention provides a method for the treatment of a respiratory disorder comprising the step of administering a pharmaceutically effective amount of a pharmaceutical formulation to a mammal such as, for example, a human. For the purposes of the invention, the term "pharmaceutically effective amount" is to be broadly interpreted and encompass the treatment of the disorder. In one embodiment, the administration is carried out via an inhalation device described herein. In one embodiment, the administration is carried out by nasal or oral inhalation.

The invention offers potential advantages relative to the prior art. As one example, the invention allows for improved control of particle size distribution of the lactose formed by this process, i.e., a more consistent particle size distribution and/or a more consistent surface morphology of the lactose is capable of being achieved from lactose feeds independent of the particle size distribution of the lactose feed. In particular, the lactose formed by the process of the invention is capable of exhibiting a more continuous particle size distribution, i.e., very little or no gap in the particle size distribution in contrast to the distribution set forth in X. M. Zeng et al., *International Journal of Pharmaceutics*, 176 (1998) 99-110.

The present invention is highly advantageous. In one embodiment, for example, the classification cut-point can be chosen so that the coarse fraction is suitable for use in a pharmaceutical formulation without fine fraction. In one embodiment, at least a portion of the fine fraction (ranging from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight) may be combined (e.g., blended) with at least a portion of the coarse fraction (ranging from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight) such that the resulting lactose composition is suitable for use in a pharmaceutical formulation. In one

embodiment, the fine fraction may be used in a pharmaceutical formulation without any coarse fraction. With respect to the above embodiments, it is preferred that lactose be employed with sufficient fine material so as to be capable of meeting the FPMass requirements, typically 20 percent to 30 percent (weight basis) of the medicament content achieved by utilising lactose that comprises 2 percent to 10 percent (volume basis) particles less than 4.5 microns as measured by Sympatec.

In view of the above, in one embodiment, the invention may further comprise combining at least one medicament with a lactose composition to form a pharmaceutical formulation. The lactose composition in such an embodiment may comprise from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight of the coarse fraction and from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight of the fine fraction. Moreover, in one embodiment, the invention may further comprise combining at least a portion of the coarse fraction with at least a portion of the fine fraction to form a lactose composition; and thereafter combining the lactose composition with at least one medicament to form a pharmaceutical formulation. Alternatively, in one embodiment, the invention may encompass simultaneously combining: (i) from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight of coarse fraction, (ii) from 0, 5, 10, 15, 20, 25, 30, 35, 40, or 45 to 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 percent by weight of fine fraction, and (iii) at least one medicament to form a pharmaceutical formulation.

As the large majority of the small particles have been produced by milling, they all typically possess a similar surface roughness. By comparison, if lactose batches are introduced into the mill that contain particles less than a volume average size of 70 microns, then these particles will essentially pass through the mill without the need to be reduced in size by the milling action. As a consequence, these particles will still exhibit a smoother crystalline surface, compared to milled lactose particles, which in turn may lead to different interactions with the active molecules.

Thus by substantially reducing or eliminating these small crystalline particles from the feed to the mill, not only can the milled particle size be

controlled, but the particles will also exhibit a very much more uniform surface morphology.

Malvern Methodology

Malvern measurements as set forth herein are determined according to the following:

Equipment

Malvern Mastersizer, laser diffraction particle size analyser fitted with the 300mm focal length lens.
MS15 stainless steel flow-through measurement cell, 2.2 mm path width (Malvern).
MSX1 small volume presentation unit (Malvern).
Viton tubing: 4.8 mm internal diameter, 1.6 mm wall thickness (Watson-Marlow).
Viton or Neoprene tubing: approximately 15mm internal diameter, 2 mm wall thickness (Watson-Marlow).
Positive pressure or vacuum filtration equipment with 0.22 µm maximum aperture membrane filters type GV (Sartorius/Millipore).
Analytical balance (Mettler, electronic) minimum weighing capacity of 30 grams with an accuracy to 4 decimal places,
Spatulas for sample transfer.

Solvent : HPLC grade iso-octane

Test Method

This section outlines the procedure for the measurement of one batch of lactose. For each batch, it is preferred that three representative samples be measured in duplicate.

Preparation of the liquid dispersant.

For the preparation of 2 litres of liquid dispersant, dissolve with ultrasonication 0.7 g of lecithin NF in $10cm^3$ of iso-octane to produce a dispersant concentrate.

Filter sufficient iso-octane using the vacuum filtration unit and a 0.22 µm filter disc. During this filtration add the dispersant concentrate

to the solvent so that it too is filtered and mixed in. Store in a pre-cleaned Winchester solvent container (Liquid dispersant).

The filtered liquid dispersant should be stored in a solvent cupboard when not in use.

Liquid dispersant may be recycled by refiltering after analysis as from above and making up to volume with iso-octane

Preparation of the Malvern Mastersizer

Set up the following measurement parameters on the Malvern Mastersizer for the test sample :

Model type :	Model independent
Presentation code :	0503
Focal length :	300 mm
Beam active length :	2.2 mm
Gain :	Low
Trigger :	Internal
Kill data low :	0
Kill data high :	0
Shape correction :	Off
Density :	1.00

Autorun number :	0
Obscuration range :	Between 0.18 and 0.22
Sweeps for measure :	1000
Sweeps for inspect :	50

Set up the MSX1 small volume presentation unit ensuring that the total length Viton tubing from the presentation unit to the flow through cell does not exceed 30cm. Attach one end of suitably sized (int. dia. approx. 15mm) Viton or Neoprene tubing (waste tubing) to the waste drain and place the other end into a red non-chlorinated waste solvent container placed on the floor.

Flush the presentation unit and the cell through with the liquid dispersant and drain.

Refill with the iso-octane/lecithin dispersant and align the laser beam using a stirrer speed of 11 o' clock (1500 ± 100 rpm). The laser intensity should be in the "good" region.

Once the laser is aligned, it is preferred that the stirrer speed should not be altered.

Sample measurement

Add the powder sample to a presentation unit using a spatula to obtain an obscuration value within the range 0.18 to 0.22.

Allow 60 seconds to allow the dispersion to equilibrate and the obscuration value to stabilise.

Measure the particle size distribution. Repeat measurement as deemed appropriate.

Sympatec Methodology

The following teachings may be employed to arrive at the Sympatec measurements described herein:

Instrumental Parameters

Parameter	**Typical**
Measuring Range	R5: 0.5/4.5→875μm
Trigger Conditions	10s, 100ms, 0.2%ch12
Time Base	100ms
Reference measurement	10s, Single
Focus Prior to first measurement	No
Start	0s after channel 12 ≥ 0.2%
Valid	Always
Stop	5s after channel 12 ≤ 0.2%
Or After	30s real time
Dispersing Device	RODOS
VIBRI Chute	Standard chute
Gap Width	2mm
Pressure	Nominal 1.5 Bar (1.3 – 1.7 Bar acceptable)
Depression	Maximise (see LSOP/WARE/092/03 section 5.2.9).
Feed Rate	85%
Sample Weight	2g ± 1g

The Sympatec HELOS is provided with the RODOS dry powder dispersion unit and the VIBRI vibratory feeder.

In these measurements, software is used in conjunction with the measurement equipment.

For the RODOS dispersing system, the primary pressure of the injector should be adjusted using the pressure control dial. The primary pressure should be within the range 1.3 – 1.7 bar although a pressure of 1.5 bar should be aimed for at each run. The injector depression should be optimised using the adjustment ring. The direction in which the adjuster ring is turned (clockwise or anti clockwise), has no adverse effect on the depression obtained. On instruments with a RODOS/M dispersing system, the primary pressure may be adjusted using a software algorithm. The injector depression should be maximised by clicking the "Auto-adjust depr" button. The instrument should not be used if the injector depression is less than 55mbar at 1.3 - 1.7 bar.

Analysis of sample

Homogenize the sample by turning the pot slowly end-over-end at least ten times in one direction and ten times in the other direction prior to analysis. This is only necessary the first time a sample is taken from a pot.

Transfer 2 ± 1 g of the lactose sample into the funnel attached to the VIBRI using a Kartell "spoon/flat" general purpose spatula (Fisher catalogue no SMJ-410-091M, volume approximately 1.8 cm^3).

A heaped spoonful of lactose powder has been demonstrated to present a sample in the range 2.0 - 3.0g.

The invention will now be described with respect to the following examples. It should be appreciated that the examples are set forth for illustrative purposes only, and do not limit the scope of the invention as defined by the claims.

Example 1

Lactose Processing

Two batches of coarse crystalline lactose A were selected. These differed from each other inasmuch that they exhibited different D50's. Batch 1 had a D50 of between 110 – 130 microns and Batch 2 had a D50 of between 160 – 180 microns, as measured by Malvern laser particle sizing techniques.

Each of these batches were then separated into a fine and coarse fraction using an air classifier. The cut point was nominally about 80 microns.

In each case the fine fraction was discarded and the coarse fractions were milled in an air classifier mill (ACM) so that the D50 of the milled product was nominally 60 - 70 microns.

The milled lactose batches were then classified at a cut point of nominally 25 microns to form a fine fraction and a coarse fraction.

Suitable proportions of the coarse and fine fraction from each milled batch were blended together so that the percentage of lactose < 4.5 microns was:

(i) 6.7% +/- 0.3%; ex batch 1

(ii) 5.0% +/- 0.3%; ex batch 1

(iii) 3.3% +/- 0.3%; ex batch 1

(iv) 6.7% +/- 0.3%; ex batch 2(v) 5.0% +/- 0.3%; ex batch 2

(vi) 3.3% +/- 0.3%; ex batch 2

The above teachings are exemplified by the following protocol:

The purpose of the following development protocol is to manufacture lactose batches having the same overall particle size distribution from different feed crystalline lactose A batches.

The feed, milling, classifying, and blending of lactose may be carried out using the following:

1) A pilot scale blender capable of blending 100 kg of material ("pilot scale blender")

2) A full scale classifier, e.g., a classifier that may be employed as a stand alone device suitable for full scale production ("full scale classifier")

The following experimental method may be employed:

1. Select 2 batches of crystalline lactose A that are different from each other in their percentage of lactose that is less than 80 microns.

Crystalline Lactose A is employed as feed lactose and is made commercially available by Borculo Domo Ingredients of Borculo, Netherlands.

These are defined as batch 1, which has a D50 of between 120 – 130 microns and batch 2 that has a D50 of 170 – 180 microns. Batch 1 should have the percentage less than 15 microns greater than 3%, whereas batch 2 should have the percentage of lactose less than 15 microns as less than 1.5%.

2. Using the full scale classifier, separate each full batch as cleanly as possible into two fractions, one being < 80 microns and the other being > 80 microns. The same settings should be used for both batches and it is desirable that no changes are to be made to the settings during the classification.

3. Mill only the fraction of lactose that is > 80 microns from both batches 1 and 2. Set the mill at nominally the same as used for commercial supply however, reduce the throughput rate of the lactose so that the milling and built in classifier can act more efficiently. Once set, discard any test millings and then mill each batch of lactose> 80 microns at the same settings.

4. Using the full scale classifier, separate each milled batch as cleanly as possible into two fractions, one being nominally < 25 microns and the other being nominally > 25 microns. The same settings should be used for both batches and it is desirable no changes are to be made to the settings during the classification.

5. Recombination by blending: Using appropriate aliquots from each batch of the classified fractions, recombine the lactose in the pilot scale blender to give:

a - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.7% +/-0.3% - From feed batch 1

b - 100kgs of product which has the percentage of lactose < 4.5 microns at 5.0% +/-0.3%- From feed batch 1

c - 100kgs of product which has the percentage of lactose < 4.5 microns at 3.3% +/-0.3%- From feed batch 1

This may be repeated using lactose from the second feed batch. (d) should be as similar to (a) as possible.

d - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.7% +/-0.3%- From feed batch 2

e - 100kgs of product which has the percentage of lactose < 4.5 microns at 5.0% +/-0.3%- From feed batch 2

f - 100kgs of product which has the percentage of lactose < 4.5 microns at 3.3% +/-0.3%- From feed batch 2

6. Dispense lactose from blender into 20kg tie sealed polyethylene bags, heat sealed in a foil laminate bag and pack inside a cardboard box. Pack at least 5 boxes from each batch.

Example 2

Lactose Processing

Two batches of coarse crystalline lactose A were selected. These differed from each other inasmuch that they exhibited different D50's. Batch 1 had a D50 of between 110 – 130 microns and Batch 2 had a D50 of between 160 – 180 microns, as measured by Malvern laser particle sizing techniques.

Each of these batches were then separated into a fine and coarse fraction using an air classifier. The cut point was nominally about 80 microns.

In each case the fine fraction was discarded and the coarse fractions were milled in an air classifier mill (ACM) so that the D50 of the milled product was nominally 60 - 70 microns.

Both milled lactose batches were then put through a 150 micron sieve. This is an additional step compared to Example 1.

The milled lactose batches were then classified at a cut point of nominally 25 microns to form a fine fraction and a coarse fraction.

Suitable proportions of the coarse and fine fraction from each milled batch were blended together so that the percentage of lactose < 4.5 microns was:

(i) 6.7% +/- 0.3%; ex batch 1
(ii) 5.0% +/- 0.3%; ex batch 1
(iii) 3.3% +/- 0.3%; ex batch 1
(i) 6.7% +/- 0.3%; ex batch 2
(ii) 5.0% +/- 0.3%; ex batch 2
(iii) 3.3% +/- 0.3%; ex batch 2

The unit operation of this protocol pertains to the process of classification of feed, milling, classifying, sieving, and blending of lactose.

The following equipment may be used:

pilot scale blender

full scale classifier

The purpose of this example is to manufacture lactose batches with the same overall particle size distribution from different feed batches. This work will use the Full Scale Classifier.

The above teachings are exemplified by the following protocol:

1. Select two batches of crystalline lactose A, batch 1 that has a D50 of 120 –130 microns, and the percentage lactose less than 15 microns is greater than 3%, and batch 2 with an D50 of 170 – 180 microns and the percentage lactose less than 15 microns is less than 1.5%. For the purposes of this protocol however, the D50 range was altered such that the batch 1 D50 was from 110-130 microns and the batch 2 D50 was from 160-180 microns.

Treat each of these big bags in an identical fashion as described in stages 2 through to 5.

2. Using the full scale classifier, separate the whole batch as cleanly as possible into two fractions, one being < 80 microns and the other being > 80 microns. The same settings should be used as those used in Example 1 and it is desirable that no changes be made to the settings during the classification.

3. Mill the coarse fraction obtained from 2. Set the mill at nominally the same as used for typical lactose milling. Once the mill is set, discard any test millings and then mill the coarse fractions from the batch at the same settings.

4. Sieve the milled material through a 150-micron sieve.

5. Using the full scale classifier, separate each sieved milled batch as cleanly as possible into two fractions, one being nominally < 25 microns and the other being nominally > 25microns. These settings should remain constant during the classification of the batch.

6. Recombination by blending: Using appropriate coarse and fine aliquots from batches 1 and 2 at the end of stage 5, recombine the lactose in the pilot scale blender to give:

a - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.7% +/-0.3% - (batch 1, Fine Feed)

b - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.7% +/-0.3%- (batch 2, Coarse Feed)

No Targets for the D50 are given for these recombinations, 60 – 90 microns would be ideal.

7. Dispense lactose from blender into 20kg tie sealed polythene bags, heat sealed in a foil laminate bag and pack inside a cardboard box. Pack at least 5 boxes from each batch.

Example 3

Lactose Processing

Two batches of coarse crystalline lactose A were selected. These differed from each other inasmuch that they exhibited different D50's. Batch 1 had a D50 of between 110 – 130 microns and Batch 2 had a D50 of between 160 – 180 microns, as measured by Malvern laser particle sizing techniques.

Each of these batches were then separated into a fine and coarse fraction using an air classifier. The cut point was nominally about 80 microns.

In each case the fine fraction was discarded and the coarse fractions were milled in an air classifier mill (ACM) so that the D50 of the milled product was nominally 60 - 70 microns.

The milled lactose batches were then classified at a cut point of nominally 25 microns to form a fine fraction and a coarse fraction.

Suitable proportions of the coarse and fine fraction from each milled batch were blended together so that the percentage of lactose < 4.5 microns was:

(i) 6.3% +/- 0.3%; ex batch 1
(ii) 6.0% +/- 0.3%; ex batch 1
(iii) 5.5% +/- 0.3%; ex batch 1
(i) 6.3% +/- 0.3%; ex batch 2
(ii) 6.0% +/- 0.3%; ex batch 2
(iii) 5.5% +/- 0.3%; ex batch 2

The above teachings are exemplified by the following protocol:

The unit operation of this protocol pertains to the process of classification of feed, milling, classifying, sieving, and blending of lactose.

The purpose of the protocol set forth in this example is to manufacture lactose batches with the same overall particle size distribution from different feed batches. This work will use the full scale classifier.

The protocol is as follows:

1. Select two batches of crystalline lactose A, batch 1 that has a D50 of 120 – 130 microns, and the percentage lactose less than 15 microns is greater than 3%, and batch 2 with an D50 of 170 – 180 microns and the percentage lactose less than 15 microns is less than 1.5%. For the purposes of this protocol however, the D50 range was altered such that the batch 1 D50 was from 110-130 microns and the batch 2 D50 was from 160-180 microns.

Treat each of these big bags in an identical fashion as described in stages 2 through to 4.

2. Using the full scale classifier, separate the whole batch as cleanly as possible into two fractions, one being < 80 microns and the other being > 80 microns. The same settings should be used as those used in Example 2, these are shown in Table 3 below. It is preferable that no changes are to be made to the settings during the classification.

Table 3

	Settings	Readings	Calculated
Classifierspeed	4.1 Hz	246 rpm	
Feedrate	15 Hz	12 Rpm	250 Kg/hour
Transport air	1500 Rpm 25 Hz	min 135m3/h max 165 m3/h	
Washair	1500 Rpm 25 Hz	min 390m3/h max 450 m3/h	

3. Using the full scale classifier with the settings in Table 4, separate each milled batch as cleanly as possible into two fractions, one being nominally < 25 microns and the other being nominally > 25microns.

Table 4

	Settings	Readings	Calculated
Classifierspeed	10 Hz	600 rpm	
Feedrate	25 Hz	20 Rpm	410 KG/hour
Transport air		min 175m3/h max 235 m3/h	
Washair		min 620m3/h max 675 m3/h	
Airsystem	2100 Rpm 35 Hz		

The above settings are capable of providing batches that are approximately 80% wt/wt coarse material and 20% wt/wt fine material.

4. Recombination by blending: Using appropriate coarse and fine aliquots from batches 1 and 2 at the end of stage 3, recombine the lactose in the pilot scale blender to give:

a - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.3% +/-0.3% - From feed batch 1

b - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.0% +/-0.3%- From feed batch 1

c - 100kgs of product which has the percentage of lactose < 4.5 microns at 5.5% +/-0.3%- From feed batch 1

This to be repeated using lactose from the second feed batch.

d - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.3% +/-0.3%- From feed batch 2

e - 100kgs of product which has the percentage of lactose < 4.5 microns at 6.0% +/-0.3%- From feed batch 2

f - 100kgs of product which has the percentage of lactose < 4.5 microns at 5.5% +/-0.3%- From feed batch 2

- Use the same amounts of fines and coarse in each pair of the combinations.
- Ensure data on Malvern and Sympatec sheets agree with data in the table.

Table 5 – Particle Size Data for Typical Lactose Production

	Normal Production Data							
	Fine fraction				Coarse fraction			
Batch number	D10 fine	D50 fine	D90 fine	15 µm fine	D10 Coarse	D50 Coarse	D90 Coarse	% 15 µm coarse
1	7.9	23	53	30.5	29	84	183	4.5
2	6.9	19	43	38.9	29	79	169	4.7
3	6.6	20	51	38.5	27	81	161	5.8
4	7.6	20	53	36.4	25	77	151	5.6
5	6.6	18	44	42.7	31	82	160	6.5
6	7.7	24	51	29.9	46	92	168	1
7	7.9	21	48	32.5	45	92	169	1
8	8.2	24	52	28	40	79	143	1.5
9	8.3	25	57	27.3	46	93	167	1.3
10	7.2	20	48	34.7	34	84	138	2.5
11	7.3	20	47	35.1	46	97	184	1
12	7	18	34	39.6	46	104	205	1
13	7.4	19	42	36.9	48	101	184	0.9
14	7.7	19	40	36.5	47	101	191	0.7
15	7.7	19	40	36.5	46	102	200	0.8
16	7.8	21	47	32.2	46	94	175	0.8
17	7.5	22	56	32.2	47	94	171	0.5
18	7.5	22	56	32.2	48	94	171	0.5
19	6.5	20	45	35	29	88	184	4.6
20	6.5	20	45	38.1	52	102	185	0.6
21	6.5	20	46	38.5	48	97	188	1
22	6.5	19	42	38.7	47	105	202	1.2
23	7.3	21	45	33.7	50	100	180	0.9
24	7.1	20	44	34.9	46	92	169	1.3
25	6.9	20	43	37.4	48	95	170	0.9
26	5.8	21	49	36.9	39	83	158	2.4
27	5.9	21	51	36.4	40	82	157	2.2
28	5.7	20	45	38.9	43	91	174	1.97
29	6.9	23	54	32	34	92	185	3.2
30	6.9	23	54	32.3	33	91	184	3.8
31	6.1	22	50	35.19	51	99	181	0.75
32	6.4	22	49	34.7	50	97	180	0.9
33	6.9	24	58	31.37	50	95	176	0.91
34	6.9	18	36	40	46	100	198	0.2
35	6.5	18	40	40	42	84	158	1.1
36	6.3	18	44	40	40	81	154	1.5
37	6.8	19	43	39	43	84	158	1.1
38	6	18	42	42	40	81	155	1.4
39	6	18	41	42	42	88	168	1.5
40	7	19	43	38	44	93	182	0.8
41	6.7	19	42	39	44	94	184	0.8
42	6.2	18	40	43	42	90	180	1
43	6	17	40	43	41	85	168	1.3
44	6.4	18	40	41	42	85	165	1
45	6.9	17	37	42	40	82	161	1
46	6.9	18	40	41	40	82	162	0.9
47	6.6	17	40	42	38	87	177	1.2
48	6.8	18	45	40	38	85	173	1.2
49	6.4	17	37	45	41	86	170	1.2

	Normal Production Data							
	Fine fraction				Coarse fraction			
Batch number	D10 fine	D50 fine	D90 fine	15 µm fine	D10 Coarse	D50 Coarse	D90 Coarse	% 15 µm coarse
50	6.1	15	33	48	41	92	187	1
51	6.6	17	37	44	41	87	167	1
52	5.8	15	33	52	33	86	170	2.3
53	6	14	32	52.3	34	85	167	2
54	6.8	16	38	45.8	38	92	173	1.4
55	6.6	14	26	57	34	80	156	2.3
56	6.8	15	29	51	30	74	147	2.8
57	6.3	15	31	51	39	90	170	1.6
58	6.6	18	53	43.6	40	91	174	1.7
59	7.5	20	44	35.2	40	88	168	2.4
60	7.8	23	51	30.3	45	92	166	1.7
61	7.5	22	48	33	43	87	158	1.8
62	7.4	22	50	32.5	44	89	164	1.5
63	7.6	22	49	32.6	47	97	184	1.4
64	7.7	24	53	29.6	47	96	186	1.1
65	7.5	23	52	31.3	45	93	181	1.2
66	7	21	49	34.8	46	94	179	1.3
67	6.8	20	48	36.2	46	96	178	1.5
68	7.3	20	44	35.8	48	98	178	1.3
69	7.1	19	44	37.2	48	97	172	1.6
70	6.9	20	48	35.9	49	98	175	1.3
71	6.5	20	45	37.9	47	96	173	1.5
72	6.6	20	48	36.5	47	95	172	1.3
73	6.5	21	52	36.1	47	95	171	1.3
Mean	6.9	19.6	44.8	38.0	42.0	90.6	172.5	1.7
Std dev	0.6	2.5	6.9	5.9	6.3	7.0	13.0	1.3
%rsd	8.9%	12.7%	15.4%	15.6%	15.0%	7.8%	7.5%	75.3%

	Pre-Classified Feed Data (Malvern)							
EXAMPLE 1(Fine)	7	28	64	27.1	52	97	164	2.2
EXAMPLE 1(Coarse)	7	26	55	28.8	48	101	189	2.5
EXAMPLE 2(Fine)	7.3	26	59	28.5	49	88	153	1.5
EXAMPLE 2(Coarse)	7	26	59	30	49	93	166	2
EXAMPLE 3(Fine)	7.1	27	58	27.4	48	87	151	1.7
EXAMPLE 3(Coarse)	7	26	56	29	50	91	157	1.6
Mean of examples 1,2&3	7.1	26.5	58.5	28.5	49.3	92.8	163.3	1.9
Stdev of Examples 1,2 & 3	0.1	0.8	3.1	1.1	1.5	5.4	13.9	0.4
RSD of Examples 1,2 & 3	1.7%	3.2%	5.4%	3.8%	3.1%	5.8%	8.5%	20.2%
Mean of Examples 2 & 3	7.1	26.3	58.0	28.7	49.0	89.8	156.8	1.7
Std Dev. Of Examples 2 & 3	0.1	0.5	1.4	1.1	0.8	2.8	6.7	0.2
RSD of Examples 2 & 3	2.0%	1.9%	2.4%	3.8%	1.7%	3.1%	4.2%	12.7%

An important aspect of the parameters described within the protocols illustrated in Examples 1 through 3 is that all initial stages are the same, irrespective of the desired amount of fine lactose in the final product to be manufactured. The varying amounts of fine lactose that are desired are achieved by combining the appropriate proportions of the coarse and fines fractions and not to mill "harder" for the lactose batches that require more fine lactose in the final product. Tables 6 and 7 show the particle size for the feed Batch A crystal by both Malvern and Sympatec, that was used in these trials.

It can be seen from these three examples that all the initial stages are similar, if not identical. The only stage at which there is a change is at the blending stage, in which more fine lactose would be added to achieve the required targets at %< 4.5 microns.

Tables 6 and 7 show the particle size data for the both coarse and fine feed crystal lactose used in Examples 1, 2 and 3. (Malvern and Sympatec)

Table 6 - Particle size data of the feed lactose prior to classification - Malvern

Feed Batch	Malvern Data			
	D10	D50	D90	% < 15 microns
"Fine" Feed for Example 1	57	123	208	2
"Coarse " Feed for Example 1	86	176	284	0.8
"Fine" Feed for Example 2	53	114	208	1.14
"Coarse " Feed for Example 2	84	162	270	0.7
"Fine" Feed for Example 3	53	114	207	1.02
"Coarse " Feed for Example 3	81	161	274	0.7

Table 7 - Particle size data of the feed lactose prior to classification - Sympatec

Feed Batch	Sympatec Data			
	D10	D50	D90	% < 4.5 microns
"Fine" Feed for Example 1	40	116	188	2
"Coarse " Feed for Example 1 –	63	165	263	1.3
"Fine" Feed for Example 2	39	103	180	1.3
"Coarse " Feed for Example 2	68	150	239	1.0
"Fine" Feed for Example 3	38	102	177	1.1
"Coarse " Feed for Example 3	65	149	248	1.3

Discussion:

A range of feed lactose has been covered by choosing both coarse and fine feed lactose in each of these three examples. They contain varying amounts of lactose that would pass through the mill, essentially un-milled, and end up in packed product.

In each of the examples 1-3, the majority of these small particles are removed by a classification process so that the resultant feed material is much more uniform when presented to the mill. A target was to reduce the amount of lactose particles less than 70 microns to less than 10%. An alternative way of expressing this is that the D10 of the resulting lactose should be greater than 70 microns by Sympatec.

The results from the three examples are shown in Table 8.

Table 8 - Coarse Fraction from the Crystalline Feed Lactose after initial classification step – Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 4.5 microns**
"Fine" Feed for Example 1				
after classification	82	135	202	0.0
"Coarse" Feed for Example 1				
after classification	107	177	259	0.0
"Fine" Feed for Example 2 –				
after classification	66	125	202	0.6
"Coarse" Feed for Example 2				
after classification (Coarse)	94	160	240	0.2
"Fine" Feed for Example 3				
after classification	67	125	203	0.4
"Coarse" Feed for Example 3				
after classification	92	158	245	0.2

It can be seen from Table 8 that there were two instances in which the target for removing the fine material less than 70 microns was not quite achieved, although the values of 66 and 67 microns are close enough that they are believed to not impact on the outcome of the experiments.

Milling of the Classified Feed

Each of the coarse fractions were then milled to reduce the D50 to between 60 – 70 microns by Malvern. The values from Example 1 indicated that slightly harder milling was required, so this was adjusted for Examples 2 and 3.

The results are shown in Table 9 (Malvern) and Table 10 (Sympatec).

Table 9 – Milled "Coarse" fraction. Particle Size Data by Malvern.

	Malvern Data			
	D10	**D50**	**D90**	**% < 15 microns**
"Fine" Feed for Example 1				
after milling coarse fraction)	15	75	152	10.0
"Coarse" Feed for Example 1				
after milling coarse fraction)	13	72	169	11.4
"Fine" Feed for Example 2				
after milling coarse fraction)	15	70	141	9.9
"Coarse" Feed for Example 2				
after milling coarse fraction)	13	66	145	11.5
"Fine" Feed for Example 3				
after milling coarse fraction)	14	64	133	10.9
"Coarse" Feed for Example 3				
after milling coarse fraction)	12	61	139	13.1

Table 10– Milled "Coarse" fraction. Particle Size Data by Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 4.5 microns**
"Fine" Feed for Example 1				
after milling coarse fraction)	7.0	63	140	6.5
"Coarse " Feed for Example 1				
after milling coarse fraction)	6.3	55	151	7.3
"Fine" Feed for Example 2				
after milling coarse fraction)	7.5	59	127	6.3
"Coarse " Feed for Example 2				
after milling coarse fraction)	6.1	54	132	7.7
"Fine" Feed for Example 3				
after milling coarse fraction)	7.0	55	123	6.7
"Coarse " Feed for Example 3				
after milling coarse fraction)	5.4	48	125	8.3

Classification of the Milled Lactose

The milled lactose was then separated into a coarse and fine fraction using the same classifier as was used to separate the fine lactose from the input feed lactose. The resultant particle size data are shown in Tables 11, 12, 13 and 14.

Table 11 - Fine Fractions after Milling and Classification of the Coarse Crystalline Feed Fraction by Malvern

	Malvern Data			
	D10	**D50**	**D90**	**% < 15 microns**
"Fine" Feed for Example 1 Milled/Classified after classification	7.0	28	64	27.1
"Coarse" Feed for Example 1 Milled /Classified after classification	7.0	26	55	28.8
"Fine" Feed for Example 2 Milled/Classified after classification	7.3	26	59	28.5
"Coarse" Feed for Example 2 Milled /Classified after classification	7.0	26	59	30.0
"Fine" Feed for Example 3 Milled/Classified after classification	7.1	27	58	27.4
"Coarse" Feed for Example 3 Milled /Classified after classification	7.0	26	56	29.0

Table 12 -Coarse Fractions after Milling and Classification of the Coarse Crystalline Feed Fraction by Malvern

	Malvern Data			
	D10	**D50**	**D90**	**% < 15 microns**
"Fine" Feed for Example 1 Milled /Classified after classification	52	97	164	2.2
"Coarse" Feed for Example 1 Milled/Classified after classification	48	101	189	2.5
"Fine" Feed for Example 2 Milled /Classified after classification	49	88	153	1.5
"Coarse" Feed for Example 2 Milled/Classified after classification	49	93	166	2.0
"Fine" Feed for Example 3 Milled /Classified after classification	48	87	151	1.7
"Coarse" Feed for Example 3 Milled/Classified after classification	50	91	157	1.6

Table 13 -Fine Fractions after Milling and Classification of the Coarse Crystalline Feed Fraction by Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 15 microns**
"Fine" Feed for Example 1 Milled/Classified after classification	4.0	22	57	12.9
"Coarse" Feed for Example 1 Milled /Classified after classification	4.0	22	56	13.1
"Fine" Feed for Example 2 Milled/Classified after classification	3.4	21	52	13.9
"Coarse" Feed for Example 2 Milled /Classified after classification	3.0	20	51	15.1
"Fine" Feed for Example 3 Milled/Classified after classification	3.5	22	54	13.3
"Coarse" Feed for Example 3 Milled /Classified after classification	3.0	21	54	14.5

Table 14 - Coarse Fractions after Milling and Classification of the Coarse Crystalline Feed Fraction by Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 15 microns**
"Fine" Feed for Example 1 Milled/Classified after classification	39	90	149	2.9
"Coarse " Feed for Example 1 Milled /Classified after classification	35	93	174	2.9
"Fine" Feed for Example 2 Milled/Classified after classification	40	83	141	2.0
"Coarse " Feed for Example 2 Milled /Classified after classification	39	88	150	2.5
"Fine" Feed for Example 3 Milled/Classified after classification	40	82	139	2.1
"Coarse " Feed for Example 3 Milled /Classified after classification	43	87	146	2.1

Recombination by Blending

The Examples 1 – 3 then call for appropriate portions of the fine and coarse fractions to be blended together so that the resultant blend contains the required amount of lactose that is less than 4.5 microns. This is in order to achieve the desired value for the FPMass performance for an inhalable formulation of salmeterol xinafoate and fluticasone propionate. These target values are listed in the Examples 1-3, and the results are shown in Tables 15-17.

Table 15- Particle Size Data for final packed product from Example 1- Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 4.5 microns**
"Fine" Feed for Example 1				
Target – 3.3% +/-0.3%	28	89	150	3.4
Target – 6.7% +/-0.3%,	7	62	139	6.7
Target – 5.0% +/-0.3%	11	78	147	5.0
"Coarse " Feed for Example 1				
Target – 6.7% +/-0.3%,	7.3	66	161	6.5
Target – 5.0% +/-0.3%	10	79	167	5.2
Target- 3.3% +/-0.3%	26	91	172	3.4

It can be seen from these Example 1 data that the Sympatec targets at %< 4.5 microns were met in every case.

Table 16 -Particle Size Data for final packed product from Example 2 – Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 4.5 microns**
"Fine" Feed for Example 2 – 216014				
Target – 6.7% +/-0.3%	7.2	57	125	6.6
Target –5.0% +/-0.3%,	10	67	131	5.1
Target – 3.3% +/-0.3%	23	76	135	3.3
"Coarse" Feed for Example 2 – 216017				
Target – 6.7% +/-0.3%,	7.4	59	134	6.4
Target – 5.0% +/-0.3%	11	75	145	5.0
Target – 3.3% +/-0.3%	24	83	148	3.3

It can be seen from the Example 2 particle size data that the Sympatec targets were met in every case.

Table 17 -Particle Size Data for final packed product from Example 3- Sympatec

	Sympatec Data			
	D10	**D50**	**D90**	**% < 4.5 microns**
"Fine" Feed for Example 3				
Target – 6.3% +/-0.3%	9.0	63	129	5.5
Target – 6.0% +/-0.3%	10.0	68	132	5.1
Target – 5.5% +/-0.3%	11	70	133	4.7
"Coarse" Feed for Example 3				
Target - 6.3 +/- 0.3%	7.8	66	135	6.2
Target- 6.0 +/- 0.3%	7.9	69	137	6.1
Target- 5.5 +/- 0.3%	10.0	72	139	5.3

It can be seen from these Example 3 data that the Sympatec targets were met for the three batches stemming from the coarse feed but not for those made from the fine feed.

Averages and relative standard deviation values for the D10, D50, D90 and the %< 15 microns for both the fine and coarse fractions for conventional production were evaluated, compared to the process of the invention . These are shown in Table 17. All values are Malvern data and the normal production is all batches of the same lactose product manufactured over an 18 month period.

Table 17 - Assessment of Particle size consistency for Example 1, Example 2 and Example 3 data

Fine fraction after Classification – Malvern				
	d10	d50	d90	%<15 microns
Current Process approximately 18 months normal production (mean of 73 batches)	6.9	19.6	44.8	38.0
Example 1, 2 and 3 mean of 6 batches	7.1	26.5	58.5	28.5
RSD Current Process approximately 18 months normal production -(73 batches)	8.9%	12.7%	15.4%	15.6%
RSD Example 1, 2 and 3 -(6 batches)	1.7%	3.2%	5.4%	3.8%
Coarse Fraction after Classification – Malvern				
	d10	d50	d90	%<15 microns
Current Process approximately 18 months normal production (mean of 73 batches)	42.0	90.6	172.5	1.7
Example 1,2 and 3 mean of 6 batches	49.3	92.8	163.3	1.9
RSD Current Process approximately 18 months normal production -(73 batches)	15.0%	7.8%	7.5%	75.3%
RSD Example 1,2 and 3 -(6 batches)	3.1%	5.8%	8.5%	20.2%

The results in Table 17 show that the particle size of the coarse and fine fractions are more consistent than that obtained during normal production, despite the fact that an adjustment was made to the milling settings between Example 1 and Examples 2 and 3. If Example 1 data is eliminated from the assessment then the variation in particle size is even less as shown in Table 18.

Table 18 - Assessment of Example 2 and Example 3 data only-Malvern

Fine fraction after Classification – Malvern				
	d10	D50	D90	%<15 microns
Current Process approximately 18 months normal production (mean of 73 batches)	6.9	19.6	44.8	38.0
Example 2 and 3 mean of 4 batches	7.1	26.3	58.0	28.7
RSD Current Process approximately 18 months normal production -(73 batches)	8.9%	12.7%	15.4%	15.6%
RSD EXAMPLE 2 and 3 - (4 batches)	2.0%	1.9%	2.4%	3.8%
Coarse Fraction after Classification – Malvern				
	d10	d50	D90	%<15 microns
Current Process approximately 18 months normal production (mean of 73 batches)	42.0	90.6	172.5	1.7
Example 2 and 3 approximately 18 months normal production mean of 4 batches	49.0	89.8	156.8	1.7
RSD Current Process approximately 18 months normal production -(73 batches)	15.0%	7.8%	7.5%	75.3%
RSD Example 2 and 3 - (4 batches)	1.7%	3.1%	4.2%	12.7%

Particle Size Profiles for Example 1, Example 2 and Example 3

The full profiles for each of the three pairs of lactose made in Examples 1 and 3 are shown in **FIGS. 1-3**.

It can be seen that these three pairs of curves are reasonably similar, despite originating from a "coarse" and "fine" feed in each occasion. For a comparison **FIG. 4** shows the data form Example 2 overlaid with two normal production batches of similar lactose. These show the extremes in differing profiles that can be obtained during normal production.

Example 4

Lactose Production

The following example demonstrates the production of lactose suitable for use in inhalation formulations, which has been produced by a method that does not require the combination of any of the fine fraction to the coarse fraction.

The following experimental method may be employed:

1. Classify 2 tons of crystalline lactose A so that the majority of fine crystals < 70 microns are removed into the fine fraction.

The remaining coarse fraction must comply with the acceptance criteria shown in Table 19 below.

Table 19

Measurement are by Sympatec	%<4.5 microns	D10	D50
Coarse Fraction	<0.2%	> 70 microns	>130 microns

3. Mill only the coarse fraction of lactose targetting 60 microns +/- 3 microns for the D50 of the milled product.

4. Using pilot scale blender, separate 300kgs of the milled batch into a fine and coarse fraction using the maximum classifier wheel speed and suitable air flow parameters to achieve the lowest micron cut point that can be achieved. This will leave a coarse fraction that contains as much fine lactose as possible. (Product A)

5. Repeat 4 on another 300kg aliquot of the milled lactose, but reduce the speed of the classifier wheel and keep the air flow at the same settings. This will produce a somewhat coarser coarse fraction. (Product B)

6. Repeat 4 again on another 300kg aliquot of the milled lactose, but reduce the speed of the classifier wheel further and keep the air flow at the same settings. This again will produce an even coarser coarse fraction.(Product C)

7. Do not add any of the fine fractions to the coarse fractions, but blend each of the coarse fractions to ensure homogeneity. Dispense the blended lactose into 20kg tie sealed polyethylene bags, which are then heat sealed into a foil laminate bag.

Pack at least 7 x 20kgs boxes of each batch, and record the particle size distribution by Sympatec on the final product.

Table 20 - Results of the Classified Feed Lactose – Coarse Fraction:

Sample Number	%< 4.5 microns	D10	D50
1	0%	92.03	155.96
2	0%	93.87	159.5
3	0%	90.75	156.24
4	0%	93.28	158.26
5	0%	92.53	157.05

It can be seen from the data in Table 20 that the readings comply with the specifications detailed in Table 19.

Results for the full particle size distribution of the final products A, B & C by Sympatec are in Table 21.

Table 21

Sympatec High Size Microns	Product A	Product B	Product C
4.50	4.26	4.01	3.91
5.50	5.30	4.94	4.80
6.50	6.33	5.86	5.65
7.50	7.36	6.76	6.48
9.00	8.89	8.10	7.71
11.00	10.92	9.88	9.33
13.00	12.94	11.68	10.98
15.50	15.47	13.99	13.11
18.50	18.49	16.83	15.79
21.50	21.47	19.75	18.59
25.00	24.91	23.19	21.94
30.00	29.69	28.07	26.79
37.50	36.54	35.18	33.96
45.00	43.05	41.93	40.85
52.50	49.24	48.34	47.43
62.50	57.02	56.34	55.64
75.00	65.83	65.35	64.89
90.00	74.83	74.48	74.26
105.00	81.95	81.64	81.60
125.00	88.81	88.49	88.60
150.00	94.13	93.77	93.97
180.00	97.47	97.08	97.30
215.00	99.14	98.78	98.96
255.00	99.77	99.54	99.65
305.00	100.00	99.87	99.93
365.00	100.00	100.00	99.98
435.00	100.00	100.00	100.00
515.00	100.00	100.00	100.00
615.00	100.00	100.00	100.00
735.00	100.00	100.00	100.00
875.00	100.00	100.00	100.00

These data can also be presented graphically as shown in Figure 8. It can be seen from Figure 8 that the amount of lactose present in the region < 25 microns high size is of the same order as that shown in Figure 4 which is that of routine commercial batches used for inhalation grade lactose. Thus, these coarse fractions are believed to be capable of displaying suitable Fine Particle Mass (FPM) performance to make them useful as inhalation grade lactose.

Conclusions:

All of the trials, Example 1, Example 2 and Example 3 have been assessed for CI performance at release and upon accelerated ageing at 25 degrees Celsius, 75% relative humidity. The series of Tables 22A, 22B and 22C show the initial mean data that were obtained during the stability study for Fine Particle Mass (FPMass), Throat, Pre-separator and stage 0, (TP0) and Stages 3+4.

Table 22A i Initial Mean Fine Particle Mass Data for 75 µg salmeterol xinafoate (equivalent to 50 µg salmeterol base) and 100 µg fluticasone propionate formulation using a conventional fine lactose

DP Trial	Fine Particle Mass (FP)	Fine Particle Mass (SX)
Example 1 – (fine lactose) ex Coarse feed	28.6	12.4
Example 1 – (fine lactose) ex Fine feed	31.8	13.9
Example 2 – (fine lactose) ex Coarse feed	26.3	12.9
Example 2 – (fine lactose) ex Fine feed	25.6	12.4
Example 3 – (fine lactose) ex Coarse feed	22.7	10.3
Example 3 – (fine lactose) ex Fine feed	21.3	10.4

Table 22A ii Initial Mean TPO Data for 50µg salmeterol base/100 µg fluticasone propionate formulation sing a conventional fine lactose

DP Trial	TPO (FP)	TPO (SX)
Example 1 – (fine lactose) ex Coarse feed	64.4	32.9
Example 1 – (fine lactose) ex Fine feed	62.0	31.8
Example 2 – (fine lactose) ex Coarse feed	65.7	33.0
Example 2 – (fine lactose) ex Fine feed	65.9	32.8
Example 3 – (fine lactose) ex Coarse feed	68.8	34.4
Example 3 – (fine lactose) ex Fine feed	70.2	35.4

Table 22A iii Initial Mean Stages 3+4 Data for 50µg salmeterol base/100 µg fluticasone propionate formulation using conventional fine lactose

DP Trial	3+4 (FP)	3+4 (SX)
Example 1 – fine lactose) ex Coarse feed	15.8	7.0
Example 1 – (fine lactose) ex Fine feed	18.0	8.1
Example 2 – (fine lactose) ex Coarse feed	14.4	7.2
Example 2 – (fine lactose) ex Fine feed	13.9	6.9
Example 3 – (fine lactose) ex Coarse feed	11.9	5.4
Example 3 – (fine lactose) ex Fine feed	11.9	5.7

NB. Specifications for Advair 50/100 are:

FP FPMass, 21 – 30; SX FPMass, 9 – 13

FP Stages 3 + 4, 11 – 19; SX Stages 3 + 4, 4 – 8

FP TP0, 55 – 80; SX TP0, 28 – 42

Table 22B i Initial Mean Fine Particle Mass Data for 50µg salmeterol base/250 µg fluticasone propionate formulation using a conventional medium grade lactose

DP Trial	Fine Particle Mass (FP)	Fine Particle Mass (SX)
Example 1 – (Medium Lactose) ex Coarse feed	57.8	10.5
Example 1 – (Medium Lactose) ex Fine feed	55.7	10.4
Example 3 – (Medium Lactose) ex Coarse feed	68.8	13.3
Example 3 – (Medium Lactose) ex Fine feed	50.3	9.7

Table 22B ii Initial Mean TPO Data for 50µg salmeterol base/250 µg fluticasone propionate formulation using a medium grade lactose

DP Trial	TPO (FP)	TPO (SX)
Example 1 – (Medium Lactose) ex Coarse feed	170.5	34.0
Example 1 – (Medium Lactose) ex Fine feed	174.8	35.2
Example 3 – (Medium Lactose) ex Coarse feed	154.7	32.1
Example 3 – (Medium Lactose) ex Fine feed	168.8	33.2

Table 22B iii Initial Mean Stages 3+4 Data for 50µg salmeterol base/250 µg fluticasone propionate formulation using a conventional medium grade lactose

DP Trial	Stages 3+4 (FP)	Stages3+4 (SX)
Example 1 – (Medium Lactose) ex Coarse feed	32.7	6.0
Example 1 – (Medium Lactose) ex Fine feed	30.2	5.7
Example 3 – (Medium Lactose) ex Coarse feed	40.0	7.8
Example 3 – (Medium Lactose) ex Fine feed	27.2	5.2

NB. Specifications for Advair 50/250 are:

FP FPMass, 51 – 75; SX FPMass, 9 – 13

FP Stages 3 + 4, 29 – 48; SX Stages 3 + 4, 5 – 8

FP TP0, 140 – 200; SX TP0, 28 – 42

Table 22C i Initial Mean Fine Particle Mass Data for 50µg salmeterol base/500 µg fluticasone propionate formulation using a conventional coarse grade lactose

DP Trial	Fine Particle Mass (FP)	Fine Particle Mass (SX)
Example 1 – (Coarse Lactose) ex Coarse feed	74.9	7.1
Example 1 – (Coarse Lactose) ex Fine feed	85.0	7.9
Example 3 – (Coarse Lactose) ex Coarse feed	125.7	12.7
Example 3 – (Coarse Lactose) ex Fine feed	123.5	11.9

Table 22C ii Initial Mean TPO Data for 50µg salmeterol base/500 µg fluticasone propionate formulation using a conventional coarse grade lactose

DP Trial	TPO (FP)	TPO (SX)
Example 1 – (Coarse Lactose) ex Coarse feed	399.2	39.3
Example 1 – (Coarse Lactose) ex Fine feed	392.1	38.8
Example 3 – (Coarse Lactose) ex Coarse feed	293.1	33.4
Example 3 – (Coarse Lactose) ex Fine feed	323.0	32.3

Table 22C iii Initial Mean Stages 3+4 Data for 50µg salmeterol base/500 µg fluticasone propionate formulation using a conventional coarse grade lactose

DP Trial	Stages 3+4 (FP)	Stages 3+4 (SX)
Example 1 – (Coarse Lactose) ex Coarse feed	42.4	4.0
Example 1 – (Coarse Lactose) ex Fine feed	49.0	4.5
Example 3 – (Coarse Lactose) ex Coarse feed	74.2	7.5
Example 3 – (Coarse Lactose) ex Fine feed	78.5	7.6

NB. Specifications for Advair 50/500 are:

FP FPMass, 106 – 150; SX FPMass, 10 – 14.

FP Stages 3 + 4, 60 – 95; SX Stages 3 + 4, 5 – 9.
FP TP0, 290– 400; SX TP0, 28 – 42.

Taking all of the factors into account, the data suggests that the pre-classification of the feed crystal to remove small lactose crystals below approximately 70 microns does not appear to significantly alter the performance ex device when compared to the normal method of lactose production. Additionally, and advantageously, the invention offers a process for forming lactose which provides improved control of particle size distribution relative to conventional processes.

Example 5

Stability Tests

Stability data for various formulations each containing 100 µg fluticasone propionate and 50 µg salmeterol base along with lactose formed in accordance with the invention were evaluated under naked conditions at 25°C and 75 percent Relative Humidity. As shown in Table 23, such data were evaluated at different time points. As shown, formulations made from the process according to the invention exhibit good stability characteristics.

Table 23

Advair Strength	Experiment Number	Conditions: Temp / %RH	Time point (months)	SX Fine Particle Mass	FP Fine Particle Mass
100/50	1		initial	12.38	28.55
100/50	1	25/75	0.5	12.53	27.74
100/50	1	25/75	1.0	12.87	28.72
100/50	1	25/75	1.5	12.22	27.34
100/50	1	25/75	2.0	12.05	27.61
100/50	1	25/75	3.0	11.45	25.77
100/50	1		initial	13.87	31.81
100/50	1	25/75	0.5	13.14	30.60
100/50	1	25/75	1.0	12.97	29.29
100/50	1	25/75	1.5	13.11	29.61
100/50	1	25/75	2.0	13.23	30.77
100/50	1	25/75	3.0	12.29	27.83
100/50	2		initial	12.42	25.60
100/50	2	25/75	2.0	11.59	24.64
100/50	2	25/75	3.0	11.34	24.24
100/50	2		initial	12.92	26.31
100/50	2	25/75	2.0	11.80	24.88
100/50	2	25/75	3.0	10.84	23.04
100/50	3		initial	10.27	22.69
100/50	3	25/75	0.5	11.65	24.27
100/50	3	25/75	1.0	10.84	24.92
100/50	3	25/75	1.5	10.59	22.21
100/50	3	25/75	3.0	10.23	21.86
100/50	3		initial	10.43	21.32
100/50	3	25/75	0.5	9.06	19.21
100/50	3	25/75	1.0	10.05	21.11
100/50	3	25/75	1.5	8.61	18.38
100/50	3	25/75	3.0	8.21	17.45

Examples 6-8

Stability Studies

Examples 6-8 set forth various pharmaceutical formulations for which the stability was evaluated. Batches 01, 02 and 03 were processed in accordance with the present invention by employing a pre-classification stage prior to proceeding by conventional manufacturing used for making Advair® made commercially available by GlaxoSmithkline of Brentford, United Kingdom. Batch 04 was made using an Advair® manufacturing process. In Tables 24-28, the symbol "T" indicates that the particle size distribution of salmeterol xinafoate and fluticasone propionate were evaluated by Cascade Impaction according to Method STM-195.

Tables 29-31 illustrate the average change of drug recovered in stages 1 to 5 as a percentage, normalising the results to take into account the total drug recovery for each device. The change is determined between the initial and final time points as defined in the protocol and is calculated according to the following equation:

$$\frac{\text{Stage 1 to 5 recovery at initial}}{\text{Total recovery at initial point}} \times 100 - \frac{\text{Stage 1 to 5 recovery at final time point}}{\text{Total recovery at final time}} \times 100$$

Tables 32-34 provide summaries of the stability studies that are set forth in Tables 35 to 130. These tables illustrate Cascade Impaction results.

Referring to the tables that follow:

"500/50 μg" refers to a formulation containing 50 μg salmeterol base and 500 μg fluticasone propionate in lactose.

"250/50 μg" refers to a formulation containing 50 μg salmeterol base and 250 μg fluticasone propionate in lactose.

"100/50 μg" refers to a formulation containing 50 μg salmeterol base and 100 μg fluticasone propionate in lactose.

"MDPI" refers to a multidose dry powder inhaler.

A* refers to in-use testing. Devices to be removed from 25°C/60% RH storage and overwrappers to be removed. Samples to be returned to storage at 25°C/75% RH. See Tables 25 and 27.

In Tables 32-34, Batches A, E and I correspond to batch 01. Batches B, F and J correspond to batch 02. Batches C, G and K correspond to batch 03. Batches D, H and L correspond to batch 04.

Tables 24-25: Testing Protocols for 100/50 µg

Table 24

Storage condition	Storage time (months)									
°C/% RH	Initial	0.5	1	1.5	3	6	9	12	14	15
	T									
25/60 Wrapped			T		T	T	T	T	A*	T
25/75 Naked		T	T	T	T					

Table 25

Storage condition	Storage time (months)			
°C/% RH [Total time on test]	0 [14]	0.5 [14.5]	1 [15]	1.5 [15.5]
25/75 Naked	T	T	T	T

Table 26: Testing Protocol for 250/50 µg

Storage condition	Storage time (months)									
°C/% RH	Initial	0.5	1	1.5	3	6	9	12	17	18
	T									
25/60 Wrapped			T		T	T	T	T	A*	T
25/75 Naked		T	T	T	T					

Tables 27-28 Testing Protocol for 500/50 µg

Table 27

Storage condition	Storage time (months)									
°C/% RH [Total time on test]	0 [17]		0.5 [17.5]		1 [18]			1.5 [18.5]		
25/75 Naked	T		T		T			T		
Storage condition	Storage time (months)									
°C/% RH	Initial	0.5	1	1.5	3	6	9	12	17	18
	T									
25/60 Wrapped			T		T	T	T	T	A*	T
25/75 Naked		T	T	T	T					

Table 28

Storage condition	Storage time (months)			
°C/% RH [Total time on test]	0 [17]	0.5 [17.5]	1 [18]	1.5 [18.5]
25/75 Naked	T	T	T	T

Table 29: Average Change of Drug Recovered in Stages 1-5 (100/50 µg)

Storage Condition/Drug	Batch			
	01	02	03	04
25°C/60%RH Wrapped SX	-5	-5	-5	-5
25°C/60%RH Wrapped FP	-5	-5	-6	-6
25°C/75%RH Naked SX	-7	-3	-4	-4
25°C/75%RH Naked FP	-7	-4	-6	-5
25°C/75%RH Naked Aged In Use SX	0	+1	-2	-1
25°C/75%RH Naked Aged In Use FP	0	0	-2	-1

Table 30: Average Change of Drug Recovered in Stages 1-5 (250/50 µg)

Storage Condition/Drug	Batch			
	01	02	03	04
25°C/60%RH Wrapped SX	-5	-4	-6	-3
25°C/60%RH Wrapped FP	-6	-5	-7	-4
25°C/75%RH Naked SX	-5	-5	-4	-4
25°C/75%RH Naked FP	-5	-5	-4	-3
25°C/75%RH Naked Aged In Use SX	+1	0	-2	0
25°C/75%RH Naked Aged In Use FP	0	0	-2	-1

Table 31: Average Change of Drug Recovered in Stages 1-5 (500/50 µg)

Storage Condition/Drug	Batch			
	01	02	03	04
25°C/60%RH Wrapped SX	-5	-3	-4	-3
25°C/60%RH Wrapped FP	-5	-3	-4	-3
25°C/75%RH Naked SX	-3	-3	0	-4
25°C/75%RH Naked FP	-3	-3	-1	-4
25°C/75%RH Naked Aged In Use SX	+1	+1	0	+2
25°C/75%RH Naked Aged In Use FP	+1	0	0	+1

Table 32 Summary of Stability Studies for 100/50µg MDPI (Example 6)

Stability data table number(s)	35 to 43	44 to 50	51 to 58	59 to 66

Batch designation (methodology)	A	B	C	D
Lactose batch designation	DD	DD	EE	FF
% of lactose fines	6.7	6.7	7.0	5.6
Data presented 25/60W 25/75N 25/75N Aged In Use	15M 3M 1.5M	15M 3M 1.5M	15M 3M 1.5M	15M 3M 1.5M
Specification failures 25/60W	1*	1*	1*	0
Specification failures 25/75N	3*	5*	3*	0
Specification failures 25/75N Aged In Use	1*	0	1*	0

Table 33 Summary of Stability Studies for 250/50μg MDPI (Example 7)

Stability data table number(s)	67 to 74	75 to 82	83 to 90	91 to 98
Batch designation (methodology)	E	F	G	H

Lactose batch designation	AA	AA	BB	CC
% of lactose fines	5.2	5.2	6.4	4.7
Data presented 25/60W 25/75N 25/75N Aged In Use	18M 3M 1.5M	18M 3M 1.5M	18M 3M 1.5M	18M 3M 1.5M
Specification failures 25/60W	0	1*	3*	0
Specification failures 25/75N	2*	0	4*	0
Specification failures 25/75N Aged In Use	0	0	0	0

Table 34 Summary of Stability Studies for 500/50μg MDPI (Example 8)

Stability data table number(s)	99 to 106	107 to 114	115 to 122	123 to 130
Batch designation (methodology)	I	J	K	L
Lactose batch designation	GG	GG	GG	HH
% of lactose fines	4.5	4.5	4.5	4.2

Data presented 25/60W 25/75N 25/75N Aged In Use	18M 3M 1.5M	18M 3M 1.5M	18M 3M 1.5M	18M 3M 1.5M
Specification failures 25/60W	2	0	1	5
Specification failures 25/75N	0	0	0	2
Specification failures 25/75N Aged In Use	0	0	0	4

Table 35 Stability data for DISKUS® 100/50 μg 60 Dose Product with overwrap

Packed Batch Number: A

Storage condition 25°C/60%RH
Testing Complete

	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**15, 15** **14, 14**	12, 12 13, 13	10, 12 11, 12	12, 11 11, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 8 8, 8	7, 7 7, 7	5, 6 6, 6	6, 6 6, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 33, 33	32, 32 34, 34	30, 34 32, 34	32, 33 31, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.1, 0.1 0.0, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

Table 36 Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: A

Storage condition
25°C/60%RH

Testing Complete

	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**15, 15** **14, 14**	11, 12 12, 12	12, 11 11, 12	12, 11 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 8 8, 8	5, 6 6, 6	6, 5 5, 6	6, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 33, 33	34, 35 34, 33	35, 33 35, 34	35, 33 34, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 37. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: A

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	35, 34 33, 33	29, 29 30, 30	25, 28 26, 28	28, 26 25, 25
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	20, 20 18, 19	16, 16 17, 17	12, 14 13, 14	15, 14 14, 12
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	64, 63 63, 63	61, 62 65, 66	58, 65 62, 65	62, 64 61, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 38. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: A

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	**35, 34** **33, 33**	26, 29 28, 28	28, 27 27, 28	29, 27 27, 29
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	**20, 20** 18, **19**	13, 14 15, 14	13, 13 12, 13	15, 14 13, 14
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	64, 63 63, 63	66, 67 65, 64	66, 64 68, 66	68, 64 66, 67
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 39. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: A

Storage condition 25°C/75%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**15, 15** **14, 14**	13, 12 **14**, 13	11, 11 12, 11	**14**, 12 12, **14**	11, 11 10, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	8, 8 8, 8	7, 6 8, 8	6, 6 7, 6	7, 7 6, 7	6, 6 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 33, 33	34, 33 34, 34	32, 33 33, 33	34, 33 34, 35	36, 35 33, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.2, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

Note: NGT = Not Greater Than

(Contd)

Table 40. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: A

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	**35, 34** **33, 33**	**31**, 27 **33, 31**	29, 27 30, 26	**32**, 29 29, **32**	28, 26 25, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	**20, 20** 18, 19	18, 14 18, 18	15, 14 17, 13	17, 16 15, 17	15, 14 12, 14
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	64, 63 63, 63	65, 62 65, 64	63, 64 65, 66	65, 63 65, 67	69, 68 65, 69
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 41. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: A

Storage condition 25°C/75%RH

Testing Complete

	End of life Specification	Storage Time			
		Initial	2 weeks	1 month	1.5 months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 12 13, 12	12, 12 11, 12	12, 11 11, 11	12, 11 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 6, 6	6, 7 6, 6	5, 5 5, 5	6, 6 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 36 36, 36	33, 34 33, 34	33, 33 32, 34	35, 34 33, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Cont'd)

Table 42. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months (cont'd)

Packed Batch Number: A

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 weeks	1 month	1.5 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	28, 29 31, 28	30, 28 27, 28	28, 27 25, 26	28, 28 27, 29
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	14, 15 15, 14	15, 16 14, 14	13, 13 12, 12	14, 14 13, 14
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	67, 67 68, 69	65, 66 65, 65	65, 64 62, 66	68, 65 64, 67
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 43. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: A

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**14**, 13 **15, 14**	12, 13 12, 12	12, 11 12, 12	10, 10 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 7 8, 8	6, 6 7, 6	6, 6 6, 6	5, 5 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 34 36, 33	35, 36 34, 35	34, 34 35, 35	33, 33 33, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 44. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: B

Storage condition *25°C/60%RH*

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**14**, 13 **15, 14**	12, 13 13, 12	12, 12 12, 11	11, 12 11, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 7 8, 8	6, 6 6, 6	6, 6 6, 6	5, 6 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 34 36, 33	32, 34 32, 33	32, 33 34, 31	35, 34 33, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.0, 0.0 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 45. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: B

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	**34**, 30 **35, 33**	29, 30 29, 29	28, 27 28, 28	23, 25 27, 28
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	18, 15 18, 18	14, 15 15, 15	15, 13 13, 14	11, 12 14, 14
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	63, 66 68, 62	66, 69 65, 66	66, 65 67, 66	64, 63 64, 67
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 46. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: B

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	**34**, 30 **35, 33**	29, 30 30, 29	26, 28 29, 26	28, 28 27, 24
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	18, 15 18, 18	15, 15 14, 15	14, 14 14, 14	13, 14 13, 12
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	63, 66 68, 62	62, 66 62, 64	61, 64 67, 62	68, 65 65, 68
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Note: NGT = Not Greater Than

Table 47. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: B

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**14**, 13 **15, 14**	13, 13 13, 13	13, 12 12, 11	13, 11 13, 12	12, 12 **14**, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	8, 7 8, 8	7, 7 7, 7	7, 7 6, 6	7, 6 7, 6	6, 6 7, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 34 36, 33	33, 32 34, 33	34, 35 34, 34	35, 30 34, 30	35, 35 36, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 48. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: B

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	**34**, 30 **35, 33**	**31, 31** **31**, 30	**31**, 29 28, 28	**31**, 27 **31**, 29	28, 28 **32**, 28
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	18, 15 18, 18	16, 17 17, 16	17, 16 16, 15	16, 14 16, 15	13, 14 16, 13
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	63, 66 68, 62	63, 61 63, 62	65, 67 66, 66	67, 57 66, 58	67, 68 70, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 49. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: B

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 11, 11	12, 12 11, 11	11, 12 11, 12	11, 12 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 5 6, 5	6, 6 5, 5	5, 6 6, 6	5, 6 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 31, 35	35, 34 33, 34	34, 35 29, 33	32, 34 34, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 50. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: B

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	27, 27 27, 26	28, 29 26, 27	26, 29 28, 28	25, 28 26, 29
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	14, 13 14, 13	13, 14 13, 13	13, 14 13, 14	12, 13 12, 14
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 69 59, 68	68, 66 64, 66	64, 68 56, 65	62, 67 67, 70
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 51. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: C

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**16, 14** **14, 15**	13, 12 12, 12	12, 12 12, 12	12, 12 13, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	**9**, 8 8, 8	7, 6 6, 6	6, 6 6, 6	6, 7 6, 7
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 32, 34	33, 34 34, 34	34, 35 34, 35	34, 32 34, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 52. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: C

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**16, 14** **14, 15**	12, 11 11, 11	12, 12 13, 12	12, 12 12, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	**9**, 8 8, 8	6, 6 5, 6	6, 6 6, 6	6, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 32, 34	32, 33 32, 33	36, 37 34, 30	34, 33 33, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.0, 0.0 0.0, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 53. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: C

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	**36, 32** **33, 35**	29, 28 29, 28	28, 28 28, 28	29, 29 30, 30
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	**20**, 18 17, **20**	15, 14 14, 14	14, 14 14, 14	14, 16 15, 15
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	59, 61 59, 62	64, 63 63, 64	64, 66 65, 66	65, 63 67, 65
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 54. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: C

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	**36, 32** **33, 35**	28, 26 25, 27	28, 28 29, 29	28, 28 27, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	**20**, 18 17, **20**	14, 13 12, 13	14, 15 15, 15	13, 14 13, 13
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	59, 61 59, 62	61, 62 64, 64	67, 71 65, 59	65, 64 63, 64
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 55. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: C

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**16, 14** **14, 15**	**14,** 13 13, 13	12,12 12,13	13, 13 13, **14**	12, 12 12, 13
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	**9**, 8 8, 8	8, 7 7, 7	7,7 7,7	7, 7 7, 7	6, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 33 32, 34	34, 35 34, 34	34,34 35,35	33, 32 35, 34	35, 34 34, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.2, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.2	0.1,0.1 0.1,0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

Table 56. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: C

Storage condition 25°C/75%RH

Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	**36, 32** **33, 35**	**33, 31** **31,** 30	29,29 28,30	**31,** 29 **31, 32**	28, 27 28, 29
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	**20,** 18 17, **20**	17, 16 16, 16	15,16 15,16	16, 15 16, 17	13, 13 14, 15
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	59, 61 59, 62	64, 65 63, 63	65,64 67,66	62, 60 65, 68	65, 70 64, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 57. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: C

Storage condition 25°C/75%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 12 11, 16	12, 12 12, 12	11, 12 12, 12	12, 11 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 5, 7	6, 6 6, 6	5, 6 6, 6	6, 5 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	34, 35 32, 34	34, 35 32, 34	33, 33 33, 33	34, 35 35, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.0 0.1, 0.0	0.1, 0.1 0.1, 0.1

(Contd)

Table 58. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: C

Storage condition 25°C/75%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	29, 28 27, 30	27, 29 28, 27	26, 27 28, 28	28, 27 25, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	15, 14 13, 15	13, 14 15, 14	13, 13 14, 13	14, 13 12, 13
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 66 63, 66	67, 67 65, 64	61, 64 64, 64	66, 66 68, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 59. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: D

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 11	11, 10 10, 11	10, 10 10, 9	9, 10 9, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 6, 6	5, 5 5, 6	5, 5 5, 5	5, 5 4, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 36, 36	36, 38 36, 35	38, 38 38, 37	37, 37 35, 38
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

Note: NGT = Not Greater Than

(Contd)

Table 60. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: D

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	9 months	12 months	15 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 11	10, 9 10, 10	9, 9 10, 9	9, 9 9, 8
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 6, 6	5, 4 5, 5	4, 4 4, 3	4, 4 4, 3
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 36, 36	36, 37 37, 37	39, 38 39, 39	37, 35 37, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.1, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 61. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: D

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	28, 26 28, 26	26, 25 23, 25	24, 24 24, 23	22, 24 21, 23
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	15, 14 15, 14	13, 12 12, 13	12, 12 12, 11	11, 11 9, 11
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 68 68, 69	70, 72 70, 66	73, 74 73, 71	71, 72 68, 74
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 62. Stability data for DISKUS® 100/50 µg 60 Dose Product with overwrap

Packed Batch Number: D

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	15 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	28, 26 28, 26	24, 22 23, 23	20, 20 23, 20	21, 21 21, 19
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	15, 14 15, 14	11, 10 12, 11	8, 9 10, 8	10, 9 9, 8
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 68 68, 69	71, 71 73, 71	74, 73 76, 76	72, 69 73, 71
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 63. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: D

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 11	10, 11 11, 11	11, 11 11, 11	11, 10 11, 11	10, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	6, 6 6, 6	5, 6 5, 5	6, 6 6, 5	6, 5 6, 6	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 36, 36	36, 36 37, 38	37, 36 37, 35	35, 32 33, 36	39, 38 37, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 64. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap

Packed Batch Number: D

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	17 to 30	28, 26 28, 26	24, 26 25, 25	26, 26 27, 25	25, 25 25, 26	23, 22 22, 23
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	9 to 19	15, 14 15, 14	12, 14 13, 13	14, 14 14, 13	13, 13 14, 14	12, 11 11, 11
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 68 68, 69	69, 69 71, 71	71, 69 71, 67	68, 62 67, 69	75, 74 72, 71
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 65. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: D

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	0.5 Months	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	9, 10 10, 9	9, 10 10, 9	9, 10 9, 8	8, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	4, 5 5, 5	4, 5 4, 4	4, 5 4, 3	4, 4 4, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 37 37, 36	39, 38 38, 38	37, 38 36, 36	32, 38 34, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.1 0.1, 0.0	0.1, 0.1 0.1, 0.1

(Contd)

Table 66. Stability data for DISKUS® 100/50 µg 60 Dose Product without overwrap (Cont'd)
Samples previously stored at 25°C/60%RH with overwrap for 14 months

Packed Batch Number: D

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	0.5 Months	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	15 to 30	22, 23 23, 22	22, 24 23, 23	21, 23 22, 20	21, 22 21, 21
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	6 to 18	10, 11 11, 11	10, 11 11, 10	9, 11 10, 8	9, 10 10, 9
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	55 to 80	68, 72 72, 71	76, 76 75, 74	72, 73 70, 70	65, 74 66, 73
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 67. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: E

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 month	3 months	6 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 12	11, 11 10, 11	10, 10 11, 11	10, 8 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	7, 6 7, 7	6, 5 5, 6	5, 6 6, 6	5, 4 5, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 32 34, 34	36, 37 36, 36	35, 34 35, 36	37, 35 33, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 68. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: E

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	9 months	12 months	18 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 12	10, 10 9, 11	11, 10 10, 11	10, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	7, 6 7, 7	5, 5 5, 6	5, 5 5, 5	5, 4 4, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 32 34, 34	36, 35 33, 36	37, 35 34, 37	36, 34 34, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.1	0.1, 0.0 0.0, 0.0

(Contd)

Table 69. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: E

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 month	3 months	6 months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	66, 61 67, 69	62, 61 59, 62	55, 59 63, 63	58, 48 54, 51
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	39, 34 39, 41	32, 31 30, 32	29, 32 34, 34	29, 22 27, 26
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	159, 154 161, 161	173, 177 170, 174	169, 165 169, 173	181, 171 163, 168
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 70. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: E

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	66, 61 67, 69	60, 55 54, 62	64, 57 55, 61	56, 50 54, 54
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	39, 34 39, 41	30, 27 28, 32	31, 28 27, 29	26, 23 25, 24
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	159, 154 161, 161	177, 169 162, 173	176, 179 167, 180	174, 165 178, 177
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 71. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: E

Storage condition 25°C/75%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 month	1.5 months	3 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 11 12, 12	12, 14 11, 12	11, 11 10, 11	12, 11 11, 11	10, 10 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	7, 6 7, 7	6, 8 6, 6	5, 6 5, 6	7, 6 6, 6	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 32 34, 34	35, 44 34, 36	35, 36 35, 36	36, 34 36, 35	37, 36 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 72. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: E

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 month	1.5 months	3 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	66, 61 67, 69	64, 77 61, 65	61, 63 58, 64	68, 65 63, 64	59, 57 58, 55
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	39, 34 39, 41	35, 44 34, 36	31, 33 30, 33	38, 36 35, 35	31, 30 29, 28
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	159, 154 161, 161	159, 188 162, 165	166, 172 170, 175	172, 162 170, 168	177, 174 176, 177
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 1 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 73. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap

Packed Batch Number: E

Storage condition 25°C/75%RH

Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 Weeks	1 month	1.5 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 9, 9	10, 10 10, 10	(a) 10	10, 10 9, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	5, 5 4, 4	5, 5 5, 5	(a) 4	5, 5 4, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 37 36, 36	35, 37 37, 35	(a) 36	35, 36 35, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.1 0.1, 0.1	(a) 0.0	0.1, 0.1 0.1, 0.1

(Contd)

Table 74. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap (cont'd)

Packed Batch Number: E

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 month	1.5 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	57, 56 54, 54	58, 56 57, 55	(a) 57	55, 57 52, 55
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	29, 26 25, 25	27, 26 27, 26	(a) 25	28, 30 25, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	170, 182 176, 175	171, 178 178, 168	(a) 182	171, 178 174, 184
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	(a) 0	0, 0 0, 0

Table 75. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: F

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	13, 12 13, 12 12, 12	12, 11 11, 11	11, 11 11, 11	11, 9 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 7 7, 7 7, 7	7, 7 6, 6	6, 6 6, 6	5, 4 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 35 36, 35 36, 33	36, 35 36, 35	35, 35 33, 31	36, 34 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.1 0.1, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 76. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: F

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	13, 12 13, 12 12, 12	11, 11 11, 12	9, 10 9, 10	9, 10 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 7 7, 7 7, 7	6, 6 5, 6	4, 4 4, 5	4, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 35 36, 35 36, 33	34, 36 36, 36	35, 37 36, 38	37, 35 35, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.1

(Contd)

Table 77. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: F

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**76**, 70 73, 70 68, 72	67, 65 62, 61	63, 61 64, 63	62, 53 61, 58
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**46**, 40 43, 42 39, 41	39, 39 36, 35	34, 33 36, 34	32, 26 31, 28
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	173, 170 170, 168 174, 159	176, 169 172, 172	170, 171 163, 154	175, 166 177, 180
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 0 1, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 78. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: F

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**76**, 70 73, 70 68, 72	65, 65 63, 68	50, 55 51, 59	54, 55 55, 57
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**46**, 40 43, 42 39, 41	33, 33 31, 35	22, 26 24, 27	25, 27 27, 28
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	173, 170 170, 168 174, 159	166, 178 175, 175	172, 180 180, 187	180, 170 172, 167
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 0 1, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 79. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: F

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	13, 12 13, 12 12, 12	11, 12 11, 11	11, 11 12, 11	10, 12 11, 12	9, 10 10, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	8, 7 7, 7 7, 7	7, 7 7, 7	6, 6 7, 6	5, 6 6, 6	5, 5 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 35 36, 35 36, 33	36, 36 36, 36	36, 36 35, 39	32, 36 37, 36	37, 37 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 80. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: F

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**76**, 70 73, 70 68, 72	65, 67 65, 65	65, 64 66, 65	59, 68 65, 67	53, 60 59, 62
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**46**, 40 43, 42 39, 41	38, 39 37, 39	37, 37 40, 35	31, 37 35, 37	26, 31 30, 33
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	173, 170 170, 168 174, 159	174, 173 172, 171	175, 174 168, 188	152, 175 178, 173	178, 180 176, 179
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 0 1, 0 0, 0	0, 0 0, 0	1, 0 1, 0	0, 0 0, 0	0, 0 0, 0

Table 81. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap

Packed Batch Number: F

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 9, 10	10, 10 10, 10	10, 10 10, 10	10, 10 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	5, 5 5, 5	5, 5 5, 5	5, 5 5, 5	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 34, 36	38, 37 36, 37	37, 38 35, 38	37, 37 34, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.0 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.1, 0.0	0.1, 0.1 0.1, 0.1

(Contd)

Table 82. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap (cont'd)

Packed Batch Number: F

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	59, 57 53, 59	55, 56 55, 57	59, 58 58, 59	55, 60 57, 61
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	30, 29 27, 31	26, 28 27, 28	28, 27 29, 29	28, 30 28, 30
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	177, 180 169, 180	185, 183 179, 186	183, 187 174, 184	180, 182 170, 181
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 83. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: G

Storage condition 25°C/60%RH

Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**15, 15** **15, 16**	13, 12 12, 13	13, 13 12, **14**	10, 12 11, 12
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	**9, 9** **9, 9**	7, 7 7, 8	7, 7 6, 7	5, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	32, 33 34, 35	32, 33 32, 32	33, 36 33, 35	30, 34 31, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 84. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: G

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • *Individual*	7 to 13	**15, 15** **15, 16**	12, 12 11, 11	13, **14** 13, **14**	11, 11 11, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	**9, 9** **9, 9**	6, 7 6, 6	7, 7 7, 7	6, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	32, 33 34, 35	33, 32 32, 33	33, 34 34, 33	33, 33 32, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 85. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: G

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**87, 86** **88, 92**	72, 68 70, 74	**77**, 74 70, **78**	57, 69 66, 72
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**52, 48** **53, 54**	42, 38 41, 44	43, 40 37, 42	29, 35 36, 37
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	152, 157 159, 165	153, 158 150, 150	160, 174 157, 168	150, 166 150, 161
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 1 1, 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 86. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: G

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**87, 86 88, 92**	70, 70 63, 65	**75, 77** 73, **75**	66, 66 65, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**52, 48 53, 54**	37, 38 32, 33	39, 42 38, 40	33, 34 33, 33
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	152, 157 159, 165	157, 152 155, 159	160, 163 165, 162	161, 164 158, 168
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 1 1, 1	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 87. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: G

Storage condition 25°C/75%RH

Testing Complete

Test	End of life	Storage Time

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	Specification	Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	**15, 15** **15, 16**	13, **14** **14**, 13	12, 13 12, 12	**14**, 12 12, 12	13, 11 11, 13
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	**9, 9** **9, 9**	6, 8 8, 7	7, 7 7, 6	8, 7 6, 7	7, 6 6, 7
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	32, 33 34, 35	32, 33 35, 34	32, 33 32, 33	34, 32 32, 33	32, 31 31, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.2	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 88. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: G

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	**87, 86** **88, 92**	72, **82** **81, 76**	67, 72 70, 68	**78,** 70 68, 72	**76,** 66 66, 73
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	**52, 48** **53, 54**	37, **46** 45, 41	38, 41 40, 37	44, 40 35, 38	42, 36 33, 40
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	152, 157 159, 165	155, 156 165, 160	155, 157 155, 161	163, 152 156, 160	156, 149 149, 160
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	1, 1 1, 1	0, 1 1, 1	1, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 89. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap

Packed Batch Number: G

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	12, 12 11, 11	11, 11 12, 10	13, 12 12, 11	11, 11 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 5, 5	6, 5 6, 5	7, 6 6, 6	6, 6 4, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	33, 34 33, 32	33, 33 34, 32	34, 33 34, 32	33, 32 33, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1

(Contd)

Table 90. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap (cont'd)

Packed Batch Number: G

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	71, 69 62, 62	65, 63 67, 61	73, 71 68, 65	66, 62 58, 61
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	35, 33 28, 29	33, 30 32, 30	39, 37 36, 33	36, 32 26, 31
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	160, 166 161, 154	156, 158 165, 155	167, 161 165, 157	162, 158 163, 166
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 91. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: H

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 10 12, 11	10, 10 11, 10	10, 9 10, 10	9, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 7, 6	6, 6 6, 6	5, 5 5, 5	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	38, 36 37, 36	38, 37 39, 38	39, 38 38, 38	38, 37 39, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 92. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: H

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 10 12, 11	9, 10 10, 10	10, 10 10, 10	10, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 7, 6	5, 5 5, 5	5, 5 5, 5	5, 4 4, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	38, 36 37, 36	38, 36 35, 35	38, 37 38, 38	39, 37 39, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.1	0.1, 0.0 0.1, 0.1

(Contd)

Table 93. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: H

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	61, 59 66, 62	57, 56 61, 58	57, 55 59, 57	53, 53 55, 54
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	35, 34 39, 34	32, 32 34, 32	30, 28 31, 29	29, 28 28, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	181, 170 175, 172	182, 180 188, 185	185, 181 181, 181	181, 179 189, 181
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 1, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 94. Stability data for DISKUS® 250/50 µg 60 Dose Product with overwrap

Packed Batch Number: H

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	61, 59 66, 62	55, 56 56, 58	60, 61 60, 59	55, 51 50, 51
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	35, 34 39, 34	27, 28 29, 30	31, 32 31, 31	27, 26 24, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	181, 170 175, 172	182, 177 172, 171	188, 182 183, 183	188, 183 193, 163
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 1, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 95. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: H

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 10 12, 11	10, 10 10, 10	10, 11 11, 10	9, 9 10, 10	9, 9 10, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	6, 6 7, 6	6, 6 6, 6	5, 6 6, 5	5, 5 5, 5	4, 5 5, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages *TP0 (µg per blister)* • Individual	28 to 42	38, 36 37, 36	37, 35 36, 37	36, 37 38, 37	36, 37 38, 38	39, 38 39, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 96. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap

Packed Batch Number: H

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	61, 59 66, 62	59, 58 59, 58	61, 61 61, 59	54, 54 57, 55	54, 54 59, 53
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	35, 34 39, 34	33, 34 36, 34	32, 33 32, 32	28, 28 30, 29	26, 27 31, 26
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	181, 170 175, 172	180, 170 172, 177	169, 175 180, 175	175, 179 183, 182	189, 185 189, 181
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 1 ,0	0, 1 1, 0	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0

Table 97. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap

Packed Batch Number: H

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	9, 9 10, 9	9, 9 9, 9	10, 10 9, 10	9, 10 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	3 to 8	5, 5 5, 4	5, 4 4, 5	5, 5 5, 5	4, 5 4, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	37, 37 36, 37	38, 38 38, 37	36, 36 37, 36	37, 38 35, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.0, 0.1	0.1, 0.0 0.2, 0.0

(Contd)

Table 98. Stability data for DISKUS® 250/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH for 17 months with overwrap (cont'd)

Packed Batch Number: H

Storage condition 25°C/75%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	2 weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	42 to 73	55, 54 57, 55	54, 53 51, 53	56, 55 55, 57	51, 56 51, 55
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	19 to 45	27, 27 28, 26	27, 26 24, 27	29, 28 27, 28	26, 28 23, 27
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	140 to 200	179, 184 178, 183	184, 184 188, 183	177, 179 183, 178	178, 184 175, 191
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	< 2	0, 0 0, 0	0, 0 0, 0	0, 0 0, 0	0, 0 1, 0

Table 99. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: I

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 11	11, 11 11, 10	10, 10 10, 10	10, 10 9, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 7	6, 6 6, 6	5, 5 6, 6	5, 5 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	34, 35 35, 33	31, 36 33, 34	36, 35 36, 36	33, 36 33, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 100. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: I

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months

Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 11	10, 10 10, 10	10, 9 8, 9	9, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 7	5, 5 5, 6	5, 4 4, 4	5, 4 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	34, 35 35, 33	35, 34 37, 37	37, 34 32, 36	36, 34 34, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.1 0.0, 0.0

(Contd)

Table 101. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: I

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months

Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	127, 130 129, 125	119, 122 121, 112	112, 111 117, 116	110, 114 105, 116
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 76 77, 75	70, 71 71, 62	60, 59 64, 64	60, 61 55, 63
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	325, 339 337, 322	301, 354 326, 333	349, 346 350, 349	326, 346 325, 319
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 0 1, 1	1, 1 1, 1

(Contd)

Table 102. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: I

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate *Sum of stages 1-5 (µg per blister)* • Individual	96 to 150	127, 130 129, 125	110, 110 109, 114	110, 96 **91**, 99	100, **95** 106, 104
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 76 77, 75	59, 60 59, 62	60, 50 48, 48	51, 50 57, 56
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	325, 339 337, 322	342, 332 364, 364	360, 337 313, 348	351, 335 342, 349
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	0, 0 0, 0	1, 1 1, 1

Table 103. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: I

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 11	11, 11 12, 11	10, 11 11, 11	10, 11 11, 11	10, 10 10, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 7	6, 6 7, 6	6, 7 6, 6	6, 6 6, 6	6, 6 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	34, 35 35, 33	37, 37 37, 35	35, 36 36, 36	34, 34 35, 35	36, 34 35, 33
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 104. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: I

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	127, 130 129, 125	127, 125 131, 117	116, 128 119, 127	114, 124 125, 118	118, 113 113, 105
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 76 77, 75	70, 68 73, 66	66, 73 69, 72	67, 72 71, 67	65, 64 62, 56
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	325, 339 337, 322	355, 362 358, 341	336, 352 346, 348	326, 324 337, 345	345, 332 344, 322
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 0

Table 105. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months

Packed Batch Number: I

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 9 9, 9	9, 9 10, 10	10, 10 10, 9	9, 9 9, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	6, 4 5, 5	5, 5 5, 5	5, 5 5, 5	4, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 38 36, 36	37, 36 37, 38	36, 36 35, 34	35, 34 35, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.0 0.0, 0.0	0.1, 0.0 0.1, 0.1	0.1, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Cont'd)

Table 106. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months (cont'd)

Packed Batch Number: I

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	107, 101 103, 105	101, 101 107, 112	115, 108 108, 104	105, 102 101, 108
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	70, 50 51, 53	54, 51 55, 59	62, 56 56, 55	50, 55 52, 57
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	344, 375 351, 359	361, 355 369, 375	359, 353 347, 341	344, 334 344, 353
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 0 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1

Table 107. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: J

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 11 12, 11	10, 11 10, 10	10, 11 11, 10	9, 10 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 6	6, 6 6, 6	5, 6 6, 5	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 36 35, 32	35, 34 35, 34	36, 36 36, 36	36, 37 36, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Cont'd)

Table 108. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: J

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 11 12, 11	10, 10 9, 9	10, 10 10, 10	10, 10 11, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 6	5, 5 5, 5	6, 5 6, 5	6, 5 6, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 36 35, 32	35, 33 36, 35	38, 37 37, 37	35, 35 36, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.1, 0.0

(Contd

Table 109. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: J

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	125, 124 127, 116	114, 118 114, 113	113, 124 119, 115	105, 108 110, 109
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 77 77, 70	65, 70 65, 67	61, 70 65, 60	54, 56 58, 58
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	336, 344 344, 309	338, 329 340, 325	354, 350 359, 358	363, 369 352, 341
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 0 0, 1

(Contd)

Table 110. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: J

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 months	12 months	18 months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	125, 124 127, 116	111, 108 103, 106	113, 113 115, 114	113, 108 117, 105
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 77 77, 70	59, 60 55, 57	61, 61 62, 59	64, 58 64, 56
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	336, 344 344, 309	343, 330 353, 342	363, 358 361, 367	350, 349 355, 344
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1

Table 111. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: J

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 11 12, 11	11, 11 11, 11	11, 11 11, 11	11, 11 11, 10	9, 10 10, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 7, 6	6, 6 6, 6	6, 7 6, 6	7, 7 7, 6	5, 6 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	35, 36 35, 32	35, 36 35, 35	34, 36 36, 34	34, 34 32, 34	35, 36 35, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.0	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Cont'd)

Table 112. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: J

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	125, 124 127, 116	121, 121 120, 120	118, 123 122, 118	124, 127 123, 115	103, 116 108, 117
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	75, 77 77, 70	68, 67 69, 66	71, 73 71, 70	72, 75 73, 64	54, 66 60, 66
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	336, 344 344, 309	339, 348 337, 343	325, 345 346, 331	334, 331 314, 332	341, 353 341, 361
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1

Table 113. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months

Packed Batch Number: J

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	9, 10 10, 10	10, 10 10, 10	10, 10 9, 10	10, 11 10, 10
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	4, 6 5, 5	5, 5 5, 5	5, 6 5, 5	6, 6 5, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 36 35, 36	36, 35 37, 35	35, 35 34, 36	38, 37 34, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.1 0.1, 0.1	0.1, 0.1 0.0, 0.1	0.0, 0.1 0.0, 0.1	0.1, 0.1 0.0, 0.1

(Cont'd)

Table 114. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months (cont'd)

Packed Batch Number: J

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	100, 115 108, 115	114, 105 115, 107	107, 114 99, 112	108, 117 116, 114
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	49, 61 57, 59	58, 53 60, 56	57, 63 52, 61	61, 63 60, 64
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	346, 359 341, 360	355, 341 366, 348	344, 348 338, 357	367, 365 340, 353
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	0, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1

Table 115. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: K

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 12	11, 11 11, 11	9, 11 10, 10	10 11 11, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 8, 7	6, 6 6, 6	5, 6 5, 6	6, 6 6, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 37 37, 39	35, 37 36, 36	34, 36 35, 38	36, 37 37, 34
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 116. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: K

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 12	10, 10 10, 9	10, 8 10, 9	9, 9 10, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 8, 7	6, 5 6, 5	5, 4 5, 4	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 37 37, 39	36, 38 35, 36	36, 34 38, 36	36, 36 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.1, 0.0 0.1, 0.0

(Contd)

Table 117. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: K

Storage condition 25°C/60%RH
Testing Complete

Test	End of life	Storage Time

	Specification	Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	124, 132 138, 136	118, 124 120, 119	104, 120 113, 117	113, 118 118, 104
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	76, 80 83, 81	69, 71 70, 68	54, 67 61, 63	64, 65 66, 57
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	344, 353 352, 371	356, 363 353, 349	334, 350 340, 365	353, 361 367, 337
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	0, 1 1, 1	1, 0 1, 0

(Contd)

Table 118. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: K

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	124, 132 138, 136	115, 113 111, 106	107, **85** 107, **94**	103, 103 112, 105
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	76, 80 83, 81	67, 60 64, 55	55, **41** 55, 48	57, 52 60, 56
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	344, 353 352, 371	351, 368 342, 361	356, 340 382, 359	350, 355 356, 365
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	0, 0 0, 0	1, 0 1, 1

Table 119. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: K

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	11, 12 12, 12	10, 10 12, 10	11, 11 11, 11	11, 10 11, 11	10, 11 11, 11
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	7, 7 8, 7	6, 6 7, 6	6, 6 6, 6	6, 5 6, 7	6, 6 6, 6
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 37 37, 39	34, 35 37, 36	35, 36 35, 35	35, 34 32, 38	32, 35 35, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.1 0.1, 0.1	0.1, 0.1 0.1, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 120. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: K

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	124, 132 138, 136	111, 114 129, 111	117, 121 120, 120	118, 108 125, 126	113, 121 118, 122
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	42 to 93	76, 80 83, 81	66, 68 77, 63	69, 69 70, 71	66, 58 72, 72	65, 68 65, 70
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	344, 353 352, 371	330, 340 354, 345	339, 353 339, 344	340, 329 310, 355	315, 343 345, 340
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1	1, 1 1, 2

Table 121. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months

Packed Batch Number: K

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 10, 9	9, 9 9, 9	11, 10 10, 10	10, 10 10, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	5, 5 5, 5	5, 5 5, 5	6, 5 5, 5	6, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	38, 35 37, 36	35, 36 34, 34	37, 35 36, 35	37, 36 36, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.1, 0.0 0.0, 0.0	0.0, 0.1 0.0, 0.1	0.1, 0.1 0.0, 0.1	0.0, 0.0 0.1, 0.1

(Cont'd)

Table 122. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months (cont'd)

Packed Batch Number: K

Storage condition

25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	109, 111 109, 105	100, 106 103, 102	119, 109 110, 109	108, 110 111, 103
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	58, 59 58, 54	53, 56 55, 55	62, 56 61, 61	60, 57 58, 56
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	373, 349 367, 361	351, 361 343, 340	369, 348 357, 351	365, 352 352, 347
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 0 1, 0	1, 1 1, 1	1, 1 1, 1	1, 1 1, 1

Table 123. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: L

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 10, 10	8, 8 9, 9	8, 8 8, 8	9, 8 8, 8
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	6, 6 5, 6	5, 4 5, 5	4, 4 4, 4	5, 4 4, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 34 36, 35	36, 36 37, 37	36, 37 35, 36	36, 36 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 124. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: L

Storage condition
25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 10, 10	10, 9 9, 9	8, 6 7, 7	9, 9 8, 8
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	6, 6 5, 6	5, 5 5, 5	4, 3 3, 4	5, 5 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 34 36, 35	36, 37 35, 36	36, 35 35, 36	36, 38 34, 35
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.0, 0.0

(Contd)

Table 125. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: L

Storage condition 25°C/60%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	1 Month	3 Months	6 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	116, 115 105, 108	**94, 90** 101, 104	**90, 93** **89, 92**	104, **94** **88, 93**
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	67, 70 60, 64	52, 48 54, 59	46, 49 47, 50	56, 49 44, 48
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	355, 337 348, 343	350, 355 358, 360	352, 367 342, 358	356, 354 357, 358
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 0 0, 1	0, 0 0, 0	0, 0 0, 0

(Contd)

Table 126. Stability data for DISKUS® 500/50 µg 60 Dose Product with overwrap

Packed Batch Number: L

Storage condition 25°C/60%RH
Testing Complete

Test	End of life Specification	Storage Time			
		Initial	9 Months	12 Months	18 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	116, 115 105, 108	109, 96 96, 100	**92, 71** **79, 83**	97, 97 **95, 94**
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	67, 70 60, 64	57, 51 52, 52	47, **32** **38, 40**	53, 54 52, 50
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	355, 337 348, 343	357, 361 345, 355	360, 354 347, 363	360, 381 345, 353
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 0, 1	0, 0 0, 0	1, 1 1, 1

Table 127. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: L

Storage condition 25°C/75%RH
Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	10, 10 10, 10	10, 9 9, 9	9, 9 8, 9	10, 9 10, 10	8, 7 9, 8
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	6, 6 5, 6	6, 5 5, 5	5, 5 5, 5	6, 5 5, 5	4, 4 5, 5
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 34 36, 35	38, 36 35, 37	37, 36 36, 37	36, 34 35, 36	36, 36 36, 36
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.0 0.0, 0.0	0.1, 0.1 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Contd)

Table 128. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap

Packed Batch Number: L

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time				
		Initial	2 Weeks	1 Month	1.5 Months	3 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	116, 115 105, 108	113, 102 101, 97	97, 99 **94**, 104	109, 106 109, 107	**91, 82** 97, **94**
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	67, 70 60, 64	63, 60 58, 56	53, 55 53, 59	62, 59 61, 61	48, 46 52, 51
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	355, 337 348, 343	371, 346 345, 356	359, 350 345, 357	349, 333 340, 355	354, 351 356, 356
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	1, 1 1, 1	1, 1 1, 1	0, 1 0, 1	1, 1 1, 1	0, 1 0, 0

Table 129. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months

Packed Batch Number: L

Storage condition
25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 1-5 (µg per blister) • Individual	7 to 13	8, 7 8, 8	8, 9 7, 8	9, 7 8, 8	9, 9 9, 9
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 3-4 (µg per blister) • Individual	4 to 8	4, 4 4, 4	4, 4 4, 4	4, 4 4, 4	5, 4 4, 4
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages TP0 (µg per blister) • Individual	28 to 42	36, 35 36, 36	35, 36 34, 35	34, 35 37, 35	36, 37 36, 37
Particle Size Distribution by Cascade Impaction Salmeterol Sum of stages 6,7 & F (µg per blister) • Individual	NGT 0.5	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0	0.0, 0.0 0.0, 0.0

(Cont'd)

Table 130. Stability data for DISKUS® 500/50 µg 60 Dose Product without overwrap Samples previously stored at 25°C/60%RH with overwrap for 17 months (cont'd)

Packed Batch Number: L

Storage condition 25°C/75%RH

Testing Complete

Test	End of life Specification	Storage Time			
		Initial	2 Weeks	1 Month	1.5 Months
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 1-5 (µg per blister) • Individual	96 to 150	**86, 83** **94, 91**	**86,** 96 **79, 92**	96, **83** **85, 86**	**95**, 98 97, 96
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 3-4 (µg per blister) • Individual	43 to 92	44, 43 49, 46	46, 49 **42**, 50	49, 43 43, 45	51, 47 48, 49
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages TP0 (µg per blister) • Individual	290 to 400	356, 354 353, 359	350, 364 340, 349	337, 348 371, 347	358, 371 359, 372
Particle Size Distribution by Cascade Impaction Fluticasone Propionate Sum of stages 6, 7 & F (µg per blister) • Individual	NGT 2	0, 0 0, 0	1, 1 0, 0	0, 0 0, 0	0, 0 0, 1

The invention has been described in reference to the embodiments set forth above. It should be appreciated that such embodiments are for illustrative purposes only, and do not limit the scope of the invention as defined by the claims.

THAT WHICH IS CLAIMED:

1. A process for forming lactose suitable for use in a pharmaceutical formulation, said process comprising:

providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less;

milling the plurality of lactose particles to yield a plurality of milled lactose particles with an average particle size, (D50), ranging from about 50 microns to about 100 microns; and

classifying said plurality of milled lactose particles into at least two fractions comprising a fine fraction and a coarse fraction wherein the fine fraction has an average particle size, (D50), ranging from about 3 microns to about 50 microns, and the coarse fraction has an average particle size, (D50), ranging from about 40 microns to about 250 microns.

2. The process according to Claim 1, wherein said step of providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less comprises obtaining the plurality of lactose particles from a crystallization process.

3. The process according to Claim 1, wherein said step of providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less comprises obtaining said plurality of lactose particles by sieving a source of lactose to produce the plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less.

4. The process according to Claim 1, wherein said step of providing a plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less comprises obtaining said plurality of lactose particles by classifying a source of lactose into two fractions comprising a fine fraction and said plurality of lactose particles containing no more than 10% w/w of lactose particles having a volume average particle size of about 70 microns or less.

5. The process as in any one of Claims 1 - 4, wherein the lactose is selected from the group consisting of anhydrous lactose, lactose monohydrate, and combinations thereof.

6. The process according to Claim 1, further comprising combining at least one medicament with a lactose composition to form a pharmaceutical formulation, the lactose composition comprising from 0 to 100 percent by weight of the coarse fraction and from 0 to 100 percent by weight of the fine fraction.

7. The process according to Claim 1, further comprising:

combining at least a portion of the coarse fraction with at least a portion of the fine fraction to form a lactose composition; and

combining the lactose composition with at least one medicament to form a pharmaceutical formulation.

8. The process according to Claim 1, further comprising combining: (i) from 0 to 100 percent by weight of the coarse fraction, (ii) from 0 to 100 percent by weight of the fine fraction, and (iii) at least one medicament to form a pharmaceutical formulation.

9. The process according to Claim 6, wherein the pharmaceutical formulation is a dry powder pharmaceutical formulation suitable for inhalation.

10. The process according to Claim 6, wherein said at least one medicament is selected from the group consisting of analgesics, anginal preparations, antiinfectives, antihistamines, anti-inflammatories, antitussives, bronchodilators, diuretics, anticholinergics, hormones, xanthines, therapeutic proteins and peptides, salts thereof, esters thereof, solvates thereof, and combinations thereof.

11. The process according to Claim 6, wherein the at least one medicament comprises at least one beta agonist.

12. The process according to Claim 11, wherein the at least one beta agonist is selected from the group consisting of salbutamol, terbutaline, salmeterol, bitolterol, formoterol, esters thereof, solvates thereof, salts thereof, and combinations thereof.

13. The process according to Claim 11, wherein the at least one beta agonist comprises salmeterol xinafoate.

14. The process according to Claim 11, wherein the at least one beta agonist comprises salbutamol sulphate.

15. The process according to Claim 6, wherein the at least one medicament comprises at least one anti-inflammatory steroid.

16. The process according to Claim 15, wherein the at least one anti-inflammatory steroid is selected from the group consisting of mometasone, beclomethasone, budesonide, fluticasone, dexamethasone, flunisolide, triamcinolone, esters thereof, solvates thereof, salts thereof, and combinations thereof.

17. The process according to Claim 15, wherein the at least one anti-inflammatory steroid comprises fluticasone propionate.

18. The process according to Claim 6, wherein the at least one medicament comprises at least one beta agonist and at least one anti-inflammatory steroid.

19. The process according to Claim 18, wherein the at least one beta agonist comprises salmeterol xinafoate and the at least one anti-inflammatory steroid comprises fluticasone propionate.

20. The process according to Claim 6, wherein the at least one medicament is selected from the group consisting of beclomethasone,

fluticasone, flunisolide, budesonide, rofleponide, mometasone, triamcinolone, noscapine, albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, terbutaline, tiotropium, ipatropium, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, isoetharine, tulobuterol, (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]methyl] benzenemethanol, esters thereof, solvates thereof, salts thereof, and combinations thereof.

21. The process according to Claim 6, wherein the at least one medicament is selected from the group consisting of albuterol sulphate, salmeterol xinafoate, fluticasone propionate, beclomethasone dipropionate, and combinations thereof.

22. The process according to Claim 6, wherein said pharmaceutical formulation further comprises at least one additional excipient.