Navigating Regulatory Label Requirements: A Comparison of NDA and Generic Labels

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ABSTRACT

Pharmaceutical regulatory labeling is essential for guaranteeing patient safety, effectiveness, and adherence to legal requirements. In the pharmaceutical sector, a label refers to the information on a drug or medical product's packaging. It contains crucial information needed for consumers and healthcare professionals to utilize the product safely and effectively. In this article we compared the regulatory labels for Advair Diskus® (fluticasone propionate and Salmeterol) and Flovent Diskus® (Fluticasone propionate) in terms of their safety profiles, dosage forms, indications, and possible side effects to know the difference between NDA &ANDA regulatory labels.

Flovent Diskus®, approved under an NDA, is a corticosteroid that reduces airway inflammation and is recommended for the treatment of asthma and chronic obstructive pulmonary disease. On the other hand, the generic medication Advair Diskus® offers a dual-action treatment for asthma and COPD by combining the anti-inflammatory effects of Fluticasone with the bronchodilator effects of Salmeterol, a long-acting beta-agonist.

Key words: Regulatory Labelling, Fluticasone Propionate, Asthma, COPD, Flovent Diskus®, Advair Diskus®

INTRODUCTION

Pharmaceutical regulatory labeling entails developing, reviewing, and managing crucial documents that convey vital product information to stakeholders while adhering to global regulatory requirements. This process guarantees that products, including drugs and food, meet industry standards and are safe for consumer use.[1-2].

The **Code of Federal Regulations (CFR)** is an executive department and agencies of the Federal government have a codification of the general & permanent rules published in federal register. Food and Drug administration reserved for the rules of Title 21 CFR. They contains regulations pertaining to Food, Drugs, Cosmetics, Medical Devicesother related things under the jurisdiction of the USFDA [3].

Parts of 21 CFR: [3]

S.NO	21 CFR'S Parts	Stands for
1	11	e-submission & e-Signature
2	50	Protection of Human Subjects
3	54	Financial disclosure by Clinical Investigators
4	56	Institutional Review Board
5	101	Food Labeling
6	104	Nutritional Quality guidelines for foods
7	106	Infant Formula Quality Control Procedures
8	110	cGMP Practices in manufacturing, Packaging or holding human food
9	210	cGMP Practices in manufacturing, Packaging or holding of drugs
10	211	cGMP Practices for finished Pharmaceuticals
11	225	cGMP Practices for medicated feeds.
12	312	Investigation New drug application
13	314	Application for FDA Approval to Market a New Drug
14	600-680	Biological Products

Comparison between Regulatory Label & Label:

A Regulatory label is a product that strictly adheres to government regulations and includes all mandatory information required by law for consumer safety.[1]

Label is a standard product label that may include additional marketing information beyond the legally required details, potentially with less emphasis on safety-critical aspects [(4).]

NDA-It is a New Drug Application is a request to the USFDA to market a new drug [(1).]

ANDA-It is an Abbreviated New Drug Application is a request to Food & Drug Administration to launch into a market to generic version of approved drug. ANDA process guarantees that generic medications are safe and efficient as name-brand ones [(2).]

*Fluticasone Propionate:*In 1980, fluticasone propionate received FDA approval, and in 1990, it was authorized for use in medicine. There is a generic version of it. Artificial gluco corticoids include fluticasone propionate. These medications are offered for a variety of inflammatory indications as topical, nasal, spray, and inhaler therapies.[(5).]

1) Anti-Inflammatory agents, Corticosteroids [(6)]

2) Mechanism of action: Glucocorticoid receptor Agonist[(6)]

METHODOLOGY

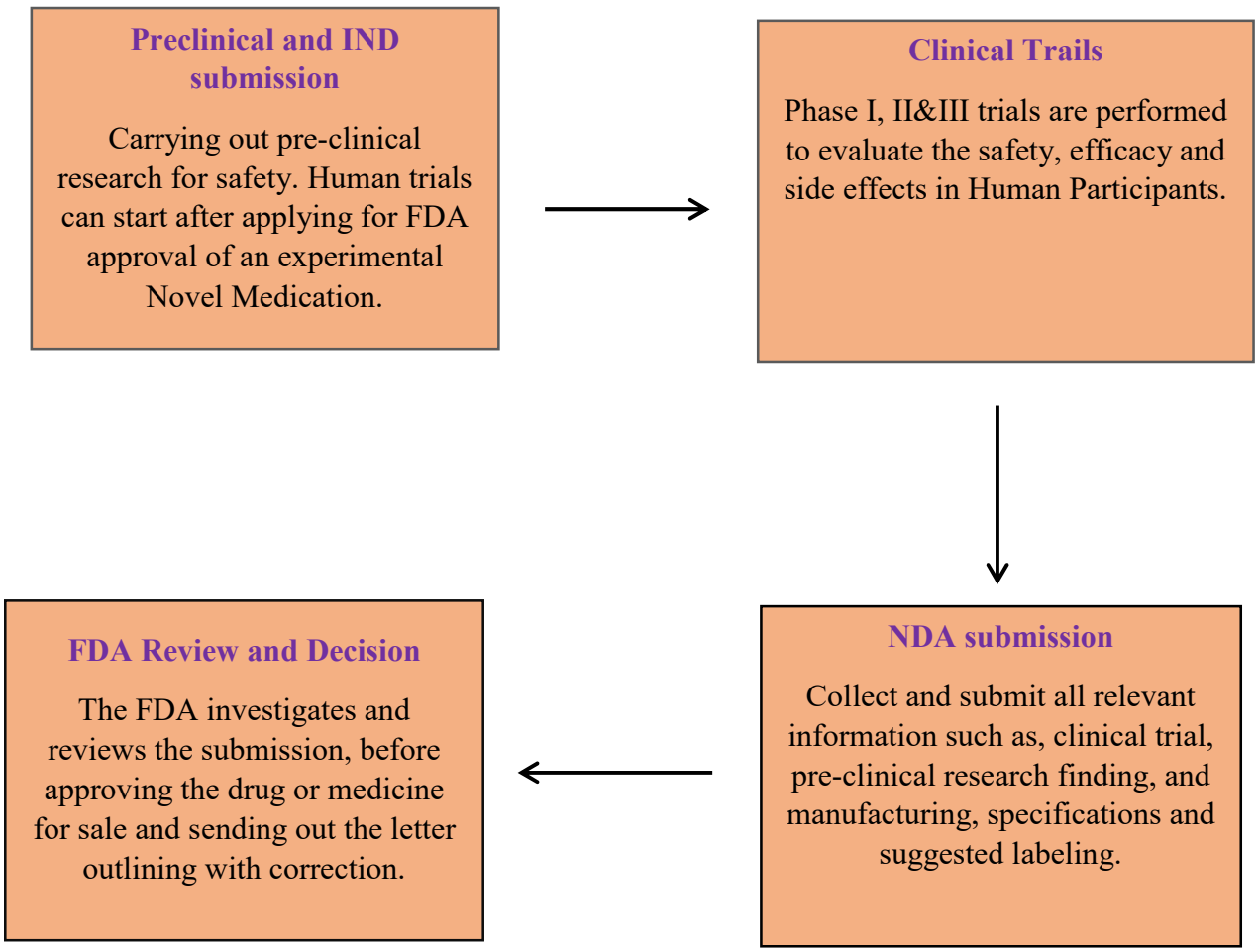
Difference between NDA & ANDA:

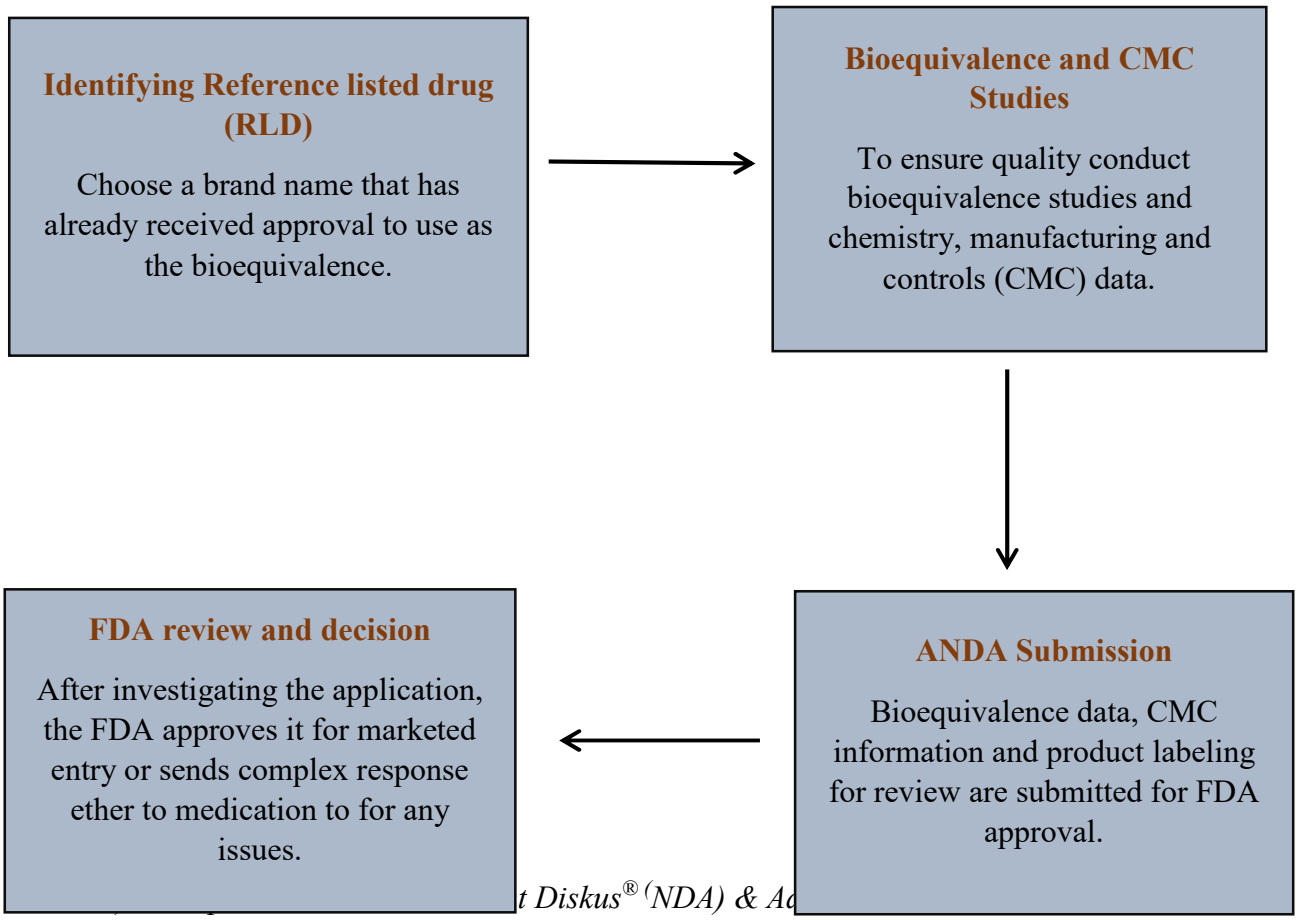
NDA	ANDA
Non-Clinical &Clinical studies are needed	BA and BE studies are needed
Section 505 (b) (2) 21 CFR 314.105 They required 3 copies of NDA are an	Section 505 (j) (2) (A) (V) 21 CFR 314.94(a) (8) They required archival, a review & a field

archival copy, a review copy & a field copy.	copies in ANDA.
Extensive review including pharmacology, Toxicology, etc.	The review process is focused mainly on bioequivalence and labeling
Form FDA-356h: application to the market a new drug biologic or antibiotics drugs for human use Form FDA- 3397- fee cover sheet user [10] Form FDA 331- NDA field report	Form FDA 3674- compliance of certification of (instrumentation included)[19] Form FDA 3794- instrumentation for completing(fee cover sheet Generic drug user)

Process of NDA & ANDA:

NDA Process:





t Diskus® (NDA) & Ac

FLOVENT DISKUS	ADVAIR DISKUS
Chemical formula: $C_{25}H_{31}F_3O_5S$	**Chemical formula:** $C_{25}H_{31}F_3O_5S$
Dosage & Administration[8]: 1) Asthma therapy & disease severity is priorly based on starting dosage. 2) 100-1000 mcg taken bis in die daily in the treatment of asthma in patients aged 12yrs an older. 3) 50-100 mcg taken bis in die daily for	**Dosage &Administration [7]:** 1. 1 inhalation 100/50, 250/50 or 500/50 doses of Advair Diskus are taken twice in a day, in the treatment of asthma for patients aged 12 & older, the severity is priorly based on starting dosage. 2. 1 inhalation of 100/50 dose of Advair Diskus is taken twice in a day, in the treatment of asthma for patients aged

the treatment of asthma in patients aged 4-11years.	4-11years. 3. 1 inhalation of 250/50 dose of Advair Diskus is taken twice in a day, in the treatment COPD.
Drug Interactions: 1. It is having potent cytochrome P450 3A4 inhibitors such as Ketoconazole & Ritonavir. 2. It may make systemic Corticosteroid effects more likely, so it is not advised to use.	**Drug Interactions:** 1. It is having potent cytochrome P450 3A4 inhibitors such as Ritonavir. 2. It may make systemic corticosteroid & Cardiovascular effect more likely, so it is not advised to use. 3. Tricyclic anti- depressants & Monoamine oxidase inhibitors are used very carefully. They may intensify he salmeterol vascular system effect. 4. Beta- blockers, it may cause severe bronchospasm by blocking the bronchodilator effects of beta-agonist. 5. Concurrent beta-agonists may create a problem in the electrodiographic abnormalities or hypokalemia that are linked with no potassium sparing diuretics hey should use carefully.

Adverse Reactions:	**Adverse Reactions :**
1. Throat irritation & upper respiratory tract infections or inflammation are incorporated. 2. Fever, Cough, Headache, Bronchitis, Sinusitis, Rhinitis, Gastrointestinal distress, Oral Candidiasis.	1. Coughing, Headaches, Nausea, Vomiting, Pharyngitis, oral candidiasis, Dysphonia bronchitis, Upper respiratory tract infections or inflammation are the symptoms of Asthma. 2. COPD symptoms include Headaches, Viral respirators, Infections, Musculoskeletal pain, throat irritation & Pneumonia.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLOVENT DISKUS safely and effectively. See full prescribing information for FLOVENT DISKUS.

FLOVENT DISKUS (fluticasone propionate inhalation powder), for oral inhalation use
Initial U.S. Approval: 1994

---------- INDICATIONS AND USAGE----------
FLOVENT DISKUS is an inhaled corticosteroid (ICS) indicated for:
- Maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older. (1)

Important limitation:
- Not indicated for relief of acute bronchospasm. (1)

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation only. (2.1)
- Starting dosage is based on prior asthma therapy and disease severity. (2.2)
- Treatment of asthma in patients aged 12 years and older: 100 mcg twice daily up to a maximum recommended dosage of 1,000 mcg twice daily. (2.2)
- Treatment of asthma in patients aged 4 to 11 years: 50 mcg twice daily up to a maximum recommended dosage of 100 mcg twice daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Inhalation powder: Inhaler containing fluticasone propionate (50, 100, or 250 mcg) as a powder formulation for oral inhalation. (3)

---------- CONTRAINDICATIONS ----------
- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate. (4)

---------- WARNINGS AND PRECAUTIONS----------
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.1)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to FLOVENT DISKUS. (5.4)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue FLOVENT DISKUS slowly. (5.5)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.7)
- Monitor growth of pediatric patients. (5.8)
- Glaucoma and cataracts may occur with long-term use of ICS. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use FLOVENT DISKUS long term. (5.9)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence >3%) include upper respiratory tract infection or inflammation, throat irritation, sinusitis, rhinitis, oral candidiasis, nausea and vomiting, gastrointestinal discomfort, fever, cough, bronchitis, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2023

Fig 1 Regulatory Labeling of Flovent Diskus® (NDA)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

ADVAIR DISKUS® 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS® 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS® 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)
FOR ORAL INHALATION

Initial U.S. Approval: 2000

WARNING: RISK OF ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). (5.1)**
- **When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. (1.1, 5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Maintenance Treatment of Chronic Obstructive Pulmonary Disease (1.2)	April 2008
Dosage and Administration, Chronic Obstructive Pulmonary Disease, (2.2)	April 2008
Warnings and Precautions, Pneumonia (5.5)	April 2008
Drug Interactions, Inhibitors of Cytochrome P450 3A4 (7.1)	April 2008

----------INDICATIONS AND USAGE----------

ADVAIR DISKUS is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Maintenance treatment of asthma in patients 4 years of age and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitations:

- Not indicated for patients whose asthma can be managed by inhaled corticosteroids with occasional use of inhaled short-acting beta$_2$-agonists. (1.1)
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

---------- DOSAGE AND ADMINISTRATION ----------

For oral inhalation only.

- Maintenance treatment of asthma in patients ≥12 years: 1 inhalation of ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of asthma in patients 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

DISKUS® device containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder. (3)

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR DISKUS. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥3%) are:

- Asthma: upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: April 2008
ADD:3PI

Fig 2 Regulatory Labeling of Advair Diskus® (Generic)

ABBREVIATIONS

NDA- New Drug Application

ANDA- Abbreviated New Drug Application

COPD- Chronic Obstructive Pulmonary Disease

CFR- Code of Federal Regulations

USFDA- United States Food & Drug Administration

cGMP - Current Good Manufacturing Practices

BA- Bioavailability

BE- Bioequivalence

RLD- Reference Listed Drug

CMC- Chemistry, Manufacturing, Controls

CONCLUSION

In order to guarantee medication safety, effectiveness, and adherence to federal rules, regulatory labeling is essential. It is clear from comparing Advair Diskus® (marketed as a generic under an ANDA) and Flovent Diskus® (NDA) that although both drugs have comparable therapeutic uses, the regulatory methods, labeling content, and review procedures are very different. ANDAs mainly concentrate on proving bioequivalence to an already-approved pharmaceutical, whereas NDAs demand a large amount of clinical, Non-clinical data. In order to guarantee that consumers receive correct product information and that it supports well-informed medical decisions, it is imperative that regulatory professionals, manufacturers, and healthcare practitioners comprehend these distinctions. Improved patient outcomes and increased confidence in the pharmaceutical regulatory system are two benefits of the standardized format and stringent label scrutiny.

ACKNOELEDGEMENT

The authors are grateful to the Guide for her helpful comments and suggestions, which have greatly improved this manuscript. We would like to express my sincere Gratitude to S.N. Vanita Maha Vidyalaya College for Women for giving us this opportunity.

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