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*APPLICATION NUMBER:*

**209482Orig1s000**

**CLINICAL REVIEW(S)**

## **Addendum to Primary Review**

**Date:** August 24, 2017  
**From:** Sofia Chaudhry, MD  
**Subject:** Addendum to Primary Clinical Review to correct errata  
**NDA:** 209482  
**Date of Submission:** November 18, 2016  
**PDUFA Goal Date:** September 18, 2017

This is an addendum to the primary clinical review for the NDA 209482 correcting the initial proposed indication statement outlined in the review. The primary clinical review states that the GSK's proposed indication is "for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease". The initial indication proposed by GSK in its NDA application was "maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema".

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/s/  
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SOFIA S CHAUDHRY  
08/24/2017

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209482
Priority or Standard	Standard
Submit Date(s)	November 18, 2016
Received Date(s)	November 18, 2016
PDUFA Goal Date	September 18, 2017
Division / Office	DPARP/ODEII
Reviewer Name(s)	Sofia Chaudhry, MD
Review Completion Date	August
Established Name	fluticasone furoate/ umeclidinium/vilanterol
(Proposed) Trade Name	Trelegy Ellipta
Therapeutic Class	ICS/LAMA/LABA
Applicant	GSK
Formulation(s)	Orally inhaled
Dosing Regimen	Once daily
Indication(s)	maintenance treatment airflow obstruction
Intended Population(s)	COPD

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The recommended regulatory action for this NDA application following modifications to the proposed labeling is: Approval.

### 1.2 Risk Benefit Assessment

GlaxoSmithKline (GSK) has submitted a 505(b)(1) NDA application for its fixed-dose, triple, dry powder inhaler containing fluticasone furoate (FF) an inhaled corticosteroid (ICS), umeclidinium (UMEC) a long-acting anti-muscarinic (LAMA), and vilanterol (VI) a long-acting beta agonist (LABA). The proposed indication is for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

The morbidity and mortality associated with COPD in the United States is substantial, with COPD reported to be the 3<sup>rd</sup> leading cause of death in the United States in 2014<sup>1</sup>. Available therapies include smoking cessation, use of supplemental oxygen in the setting of chronic hypoxemia, and pharmacologic therapies including short- and long-acting bronchodilators, inhaled and systemic corticosteroids, theophylline and phosphodiesterase-4 inhibitors. As outlined in the GOLD treatment guidelines<sup>2</sup>, patients may require therapy with all three classes of orally inhaled drugs (ICS, LABA and LAMA). In current practice, to administer this regimen, patients must use at least two separate inhalers once or twice daily in addition to use of their rescue inhaler as required. This maintenance therapy can be prescribed either as ICS/LABA combination product + a LAMA or as a LAMA/LABA combination product + ICS monotherapy<sup>3</sup>. While this treatment regimen is effective in many individuals, complex treatment regimens requiring the use of multiple inhalers have been linked with poorer clinical outcomes in patients with COPD likely due to decreased adherence<sup>4</sup>. The approval of a fixed-dose combination product containing an ICS, LABA and LAMA would provide a convenient therapeutic option for patients with the potential to improve clinical outcomes.

The efficacy data provided by GSK to support this NDA application is derived from two, 12-week studies (studies 200109 [109] and 200110 [110]) demonstrating an additive

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1 <https://www.cdc.gov/copd/index.html> accessed August 3, 2017

2 The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: <http://goldcopd.org> accessed August 3, 2017

3 There are no ICSs approved for the treatment of COPD in the United States as a monotherapy. In the United States, ICSs are approved as part of a dual combination product containing a LABA for the treatment of COPD.

4 Andrew, P. Yu, et al. "Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD." *Respiratory medicine* 105.12 (2011): 1861-1871.

lung function benefit when UMEC is added to background FF/VI therapy. Both UMEC and FF/VI are approved for the maintenance treatment of airflow obstruction in COPD (NDA 205382 approved 4/30/2014 and 204275 approved 5/10/2013 respectively), while FF/VI is also approved for exacerbation reduction in COPD. Studies 109 and 110 each demonstrate statistically significant and clinically meaning improvements in trough FEV<sub>1</sub> of approximately 120 ml when UMEC 62.5 is added to patients taking background FF/VI 100/25 therapy. These data were previously reviewed by the Agency and added to Section 14 of the Incruse USPI (NDA 205382 supplement 002, approved February 24, 2016).

Of note, studies 109 and 110 administered the triple therapy in an 'open' configuration from two separate inhalers (FF/VI + UMEC), while this NDA application is for the approval of a 'closed configuration' of FF/UMEC/VI in a single inhaler. To bridge the data between studies 109 and 110 from the 'open configuration' to the 'closed configuration' to support this application, GSK submitted adequate in-vitro and PK data demonstrating a lack of pharmaceutical differences between FF/VI + UMEC and FF/UMEC/VI. These data demonstrate that the delivery of FF, UMEC and VI delivery are the comparable whether administered as UMEC + FF/VI via two separate inhaler or from single inhaler containing FF/UMEC/VI.

Safety information for this fixed-dose, triple therapy product is provided by these same two 12-week trials and the large safety databases supporting Breo Ellipta (FF/VI; NDA 204275); Anoro Ellipta (UMEC/VI; NDA 203975) and Incruse Ellipta (UMEC; NDA 205382).

While this application does not formally address 21CFR 300.50 (the Fixed-Combination Prescription Drug Rule) by providing clinical data demonstrating the clinical benefit provided by each component of the product, the data do support a restricted indication for use in patients requiring additional bronchodilation on background FF/VI therapy. The approval of single fixed-dose triple inhaler with the restricted indication will provide patients requiring therapy with all three drug classes with a convenient treatment option while reflecting the efficacy data submitted in support of this application.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

FF/UMEC/VI is an orally inhaled dry powder delivered by an Ellipta inhaler. The Ellipta inhaler is a light grey and beige inhaler containing 2 blister strips. One strip contains a blend of micronized fluticasone furoate (100 mg) and lactose monohydrate (12.3 mg), and the second strip contains a blend of micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg of umeclidinium), micronized vilanterol trifenate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (75 mcg) and lactose monohydrate (12.3 mg). When actuated, the content of a single blister from each strip is exposed and ready for dispersion into the patient’s airstream.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple approved products containing an ICS, LAMA, LABA or some combination thereof for the treatment of COPD.

Table 1: Approved LABA, LAMA, and ICS products for COPD

	Class	Drug Substance	Trade Name
Single ingredient	Long-acting beta agonist	Salmeterol xinafoate	Serevent Diskus
		Formoterol fumarate	Foradil Aerolizer
		Arformoterol tartrate	Brovana
		Formoterol solution	Perforomist
		Indacaterol maleate	Arcapta neohaler
	Long-acting antimuscarinic	Olodaterol hydrochloride	Striverdi respimat
		Tiotropium bromide	Spiriva handihaler Spiriva respimat
		Aclidinium bromide	
		Umeclidinium bromide	
		Glycopyrrolate	Seebri
Combination	ICS/LABA	Fluticasone furoate/ salmeterol	
		Budesonide/formoterol	Symbicort
		Fluticasone furoate/vilanterol	Breo Ellipta
	LAMA/LABA	Umeclidinium/vilanterol	
		Tiotropium/olodacterol	Stiolto
		Glycopyrrolate/indacaterol	Utibron neohaler
		Glycopyrrolate/formoterol	Bevespi Aerosphere

### 2.3 Availability of Proposed Active Ingredient in the United States

All three components in the fixed dose, triple, combination product are approved for the treatment of COPD either as a monotherapy or as a component in a fixed-dose dual combination product.

**Table 2: Approved Ellipta Products for COPD**

Trade Name	Drug Substance		Dosage	Indication (s)	NDA # Approval Date
	Strip 1	Strip 2			
Breo Ellipta (FF/VI)	FF	VI	100/25 <sup>†</sup>	Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD	204275 5/10/2013
Anoro Ellipta (UMEC/VI)	UMEC	VI	62.5/25	Maintenance treatment of airflow obstruction in patients with COPD	203975 12/18/2013
Incruse Ellipta (UMEC)	UMEC		62.5	Maintenance treatment of airflow obstruction in patients with COPD	205382 4/30/2014

<sup>†</sup> one dosage strength approved for COPD, 100/25 and 200/25 are approved for asthma  
FF = fluticasone furoate; VI = vilanterol; UMEC = umeclidinium

### 2.4 Important Safety Issues With Consideration to Related Drugs

The safety profiles for an ICS, LABA and LAMA are well characterized in COPD. Major concerns with use of ICS in COPD include an increased risk of pneumonia (PNA), while LABA and LAMA therapy may impact cardiovascular function (CV).

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant and the Division had multiple interactions, including standard milestone meetings, to discuss the clinical development program for FF/UMEC/VI. The discussion points are summarized in the table below.

**Table 3: Summary of Key Regulatory Interactions**

Date	Interaction	Comments
May 7, 2012	PIND	- The Division noted that the development programs for FF/VI, UMEC/VI and UMEC COPD programs were all ongoing. It was recommended that GSK consider utilizing the GOLD criteria to identify a target population that

		requires triple therapy. The plan to conduct a single large exacerbation trial comparing the triple product to relevant comparators (UMEC/VI and FF/VI) was considered reasonable.
September 18, 2013	EOP2	<ul style="list-style-type: none"> <li>- Program should provide in-vitro and PK data to demonstrate no major pharmaceutical between the triple product and dual product comparators.</li> <li>- It was agreed that all causes of death should be adjudicated in the planned exacerbation trial.</li> <li>- GSK explored the potential for evaluating patients with elevated eosinophil counts as 'responder' population with COPD for ICS therapy. The Division noted that any subgroup analyses are at the sponsor's discretion.</li> </ul>
February 27, 2014	Written responses	<ul style="list-style-type: none"> <li>- Agency reviewed in-vitro data and found that it supported an absence of major pharmaceutical differences between the products. An increase in systemic exposure for VI with the triple product was noted, but the Division confirmed that that it was reasonable to proceed with the phase 3 trial.</li> <li>- Plan to handle missing data was found to be reasonable.</li> </ul>
November 12, 2014	Written responses	<ul style="list-style-type: none"> <li>- Plan to evaluate the decline in FEV<sub>1</sub> was discussed. The Division confirmed that it viewed this endpoint as clinically meaningful.</li> <li>- Any claims specifically targeting patients with elevated eosinophil would be dependent on demonstrating the dependence of the treatment effect on eosinophil count.</li> </ul>
February 24, 2016	Approval	<ul style="list-style-type: none"> <li>- Approval of Supplement 2 to NDA 205382 to add the results of 4 studies evaluating the added bronchodilator benefit provided when UMEC is added to patients on background ICS/LABA therapy to the UMEC USPI.</li> </ul>
May 24, 2016	Type C	<ul style="list-style-type: none"> <li>- Division stated it was reasonable to file an NDA application based on the results of studies 200109 and 200110 and in-vitro and PK data demonstrating the absence of pharmaceutical differences between the closed triple (FF/UMEC/VI) and 'open triple' (FF/VI + UMEC).</li> <li>- The Division questioned the need for data from Study CTT116583 (study comparing FF/UMEC/VI vs an unapproved bud/form comparator) and a planned 4 week lung function study between the 'open triple' and 'closed triple' given the data to support an absence of pharmaceutical differences between the open and closed triple products and the extensive safety databases for FF/VI, UMEC/VI and UMEC in COPD</li> </ul>
July 27, 2016	Written Response	<ul style="list-style-type: none"> <li>- Format and content of planned NDA discussed.</li> </ul>

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The applicant has submitted in-vitro data demonstrating the pharmaceutical comparability between FF/UMEC/VI 100/62.5/25, FF/VI 100/25 and UMEC/VI 62.5/25 and UMEC 62.5 based on Aerodynamic Particle Size Distribution (APSD) data generated using the Next Generation Impactor (NGI) at a flow rate of 60 L/minute. These data demonstrate no pharmaceutical interactions between the components providing reassurance that the delivered doses of the components of FF/UMEC/VI are the same whether it is delivered to a patient by the fixed dose triple combination product FF/UMEC/VI or through the use of two separate FF/VI and UMEC inhalers.

Readers are referred to the CMC review for additional details.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

Fluticasone furoate (FF) is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. While the precise mechanism by which FF affects COPD symptoms is not known, inflammation is known to be an important component in the pathogenesis of COPD. Corticosteroids, such as FF, have been shown to have a wide range of action on multiple inflammatory cell types and mediators. In in-vitro and in-vivo models, FF has been shown to activate the glucocorticoid response element (GRE), inhibit pro-inflammatory cytokines such as NFkB, and inhibit antigen-induced lung eosinophilia in sensitized rats.

Umeclidinium is a long-acting muscarinic antagonist. In the airways, it inhibits the M3 receptor on smooth muscle leading to bronchodilation.

Vilanterol is a long-acting beta agonist. Beta<sub>2</sub>-adrenergic agonist drugs stimulate intracellular adenylyl cyclase which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Cyclic AMP causes relaxation of bronchial smooth muscle and inhibits the release of immediate hypersensitivity mediators from mast cells.

#### 4.4.2 Pharmacodynamics

Each component in FF/VI/UMEC has been previously approved for use in COPD. As such, the expected PD effects have already been characterized, including the dual effects of VI and UMEC on cardiac rhythm in patients with COPD and impact of FF on the HPA axis. Readers are referred to the USPI Section 12.2 for UMEC/VI and FF/VI for additional information.

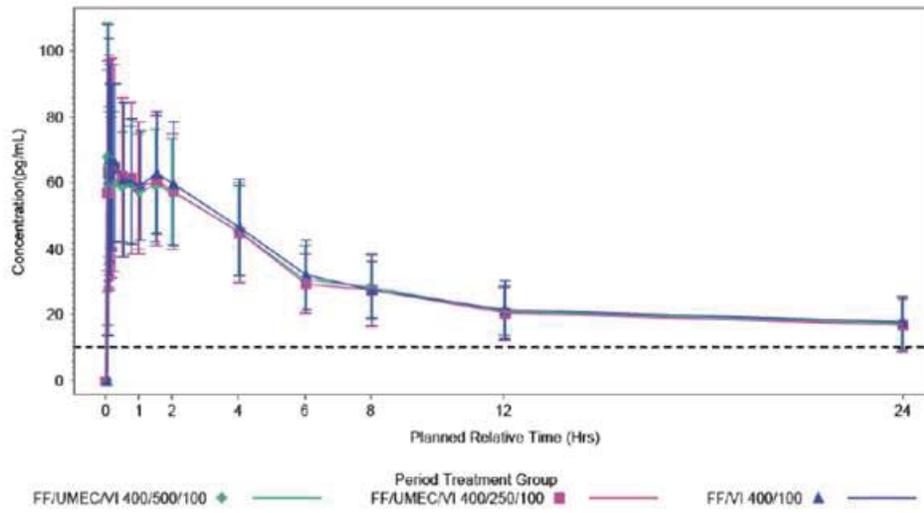
#### 4.4.3 Pharmacokinetics

The clinical pharmacology data in support of this application include data from Study CTT116415 and Study 20087. As discussed in Section 6, the data from studies 200109 and 200110 provide support for an additive lung function benefit when UMEC is added to FF/VI.

**The FF, UMEC and VI exposure data from these comparisons are presented in Figure 1, Figure 2, and**

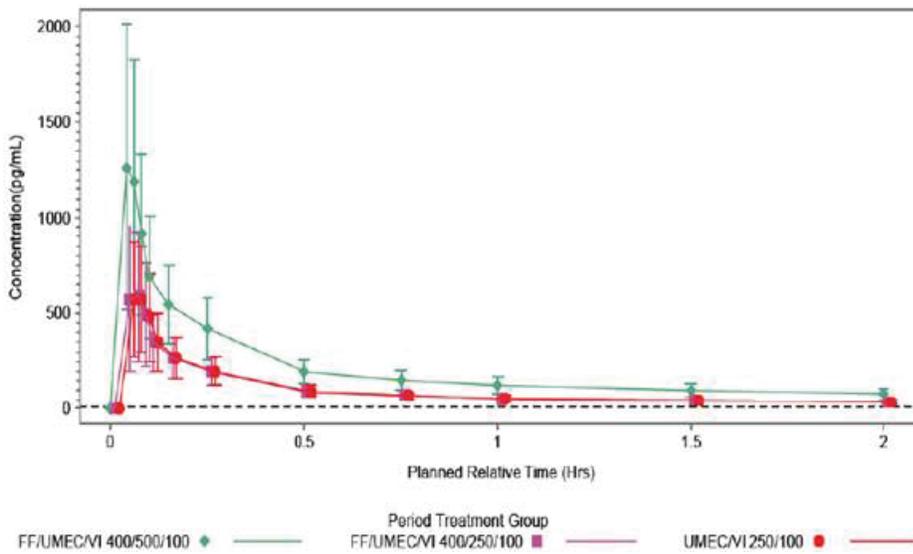
**Figure 3 respectively.** While the observed VI exposure is noted to be higher from FF/UMEC/VI compared to FF/VI and UMEC/VI, this finding was not found to be relevant during the prior clinical pharmacology review of these data for NDA 205328 supplement 2. Overall, the clinical pharmacology data from these two trials demonstrate that the systemic exposure of FF, VI and UMEC are similar when dosed as FF/UMEC/VI, FF/VI or UMEC/VI. In addition to these data, PK data from the active comparator study CTT116853 demonstrate similar systemic exposure in a COPD population. Readers are referred to the clinical pharmacology review for additional details.

Figure 1: Mean ( $\pm$ SD) FF concentration-time plots



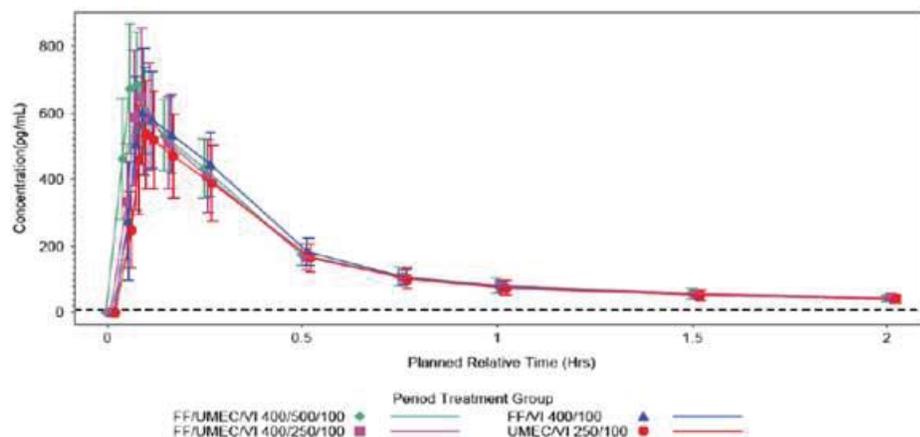
Source: Clinical Pharmacology review, NDA 205382/S2

Figure 2: Mean ( $\pm$ SD) UMEC concentration-time plots



Source: clinical pharmacology review

Figure 3: Mean ( $\pm$ SD) VI concentration-time plots



Source: Clinical Pharmacology Review

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 4: Pivotal Efficacy studies submitted to support this application

Trial	Design	Population	Tx arms (N)	Endpoints
200109	R, MC, DB, PG, 12-week treatment period	Moderate to severe COPD on OL FF/VI	UMEC 62.5 (206) UMEC 125 (207) Placebo (191)	1: Day 85 Trough FEV <sub>1</sub>  2: Day 84 WM FEV <sub>1</sub> (0-6h)
200110	R, MC, DB, PG, 12-week treatment period	Moderate to severe COPD on On OL FF/VI	UMEC 62.5 (206) UMEC 125 (208) Placebo (206)	1: Day 85 Trough FEV <sub>1</sub>  2: Day 84 WM FEV <sub>1</sub> (0-6h)

Tx = treatment; R = randomized, MC = multicenter, DB = double-blind, PG = parallel group, OL = open label; FF/VI = fluticasone furoate/vilanterol (Breo Ellipta), UMEC = umeclidinium (Incruse Ellipta), WMFEV<sub>1</sub> = weighted mean FEV<sub>1</sub>

## 5.2 Review Strategy

This application relies on data from studies 109 and 110 which demonstrate a clinically meaningful and statistically significant increase in lung function when UMEC is added to background FF/VI. These data were previously reviewed as support for a supplemental NDA application for Incruse Ellipta (NDA 205382 supplement 002) to update the USPI with the results of these studies (and results from replicate studies demonstrating an additional lung function benefit when added to Advair Diskus) to Section 14 of the Incruse USPI. For the ease of the reader for this NDA application, a summary of the trial designs, efficacy and safety data from Studies 200109 and 200110 can be found in Sections 5, 6 and 7 respectively. Readers are referred to the Clinical Review for NDA 205382 supplement 2 by this reviewer dated June 30, 2015 for additional details.

## 5.3 Discussion of Individual Studies/Clinical Trials

Studies 109 and 110 were replicate Phase 3b, multicenter, randomized, parallel group studies evaluating the addition of UMEC 62.5 or UMEC125 to stable background FF/VI therapy in subjects with moderate to severe COPD.

Eligible subjects were male or female, 40 years of age and older with a history of COPD and  $\geq 10$  year smoking history (current or former). Subjects were required to have a pre- and post-SABA  $FEV_1/FVC$  ratio  $< 0.7$  and a pre- and post-SABA  $\leq 70\%$  of predicated normal values and dyspnea score  $\geq 2$  on the mMRC at screening. Subjects with clinically significant uncontrolled disease or with an abnormal laboratory or ECG finding were excluded. All subjects were provided with a rescue SABA inhaler for PRN use.

Following a 4-week run-in period during which all subjects received open-label FF/VI 100/25, eligible subjects were randomized 1:1:1 to one of the following double-blind treatments: UMEC 62.5 mcg, UMEC 125, or placebo. There were a total of 8 clinic visits and a follow-up phone contact to obtain additional safety information 7 days after the last clinic visit.

The primary endpoint was trough  $FEV_1$  on Day 85 with post-dose weighted mean  $FEV_1(0-6hr)$  at Day 84 evaluated as secondary endpoint. Additional endpoints included an evaluation of rescue medication use, proportion of subjects achieving an increase  $\geq 100$  mL in trough  $FEV_1$ , trough  $FEV_1$  and WM  $FEV_1$  at additional time points, proportion achieving an increase  $\geq 12\%$  and  $\geq 200$  mL above baseline at any time during the 0-6h post dose on Day 1, serial  $FEV_1(0-6h)$  at each time point, peak  $FEV_1$ , and time to onset (defined as an increase  $> 100$  ml above baseline), serial and trough FVC, AEs, VS, and COPD exacerbations as well as SGRQ-C and CAT.

The primary endpoint was analyzed using intent to treat population and a step-down closed testing procedure was applied to account for multiplicity across the primary and

secondary endpoint. There was no adjustment for multiplicity for the remaining endpoints.

## 6 Review of Efficacy

### **Efficacy Summary**

The data from the replicate 12-week lung function studies 109 and 110 demonstrate a statistically significant and clinically meaningful improvement in trough FEV<sub>1</sub> of approximately 120 ml when UMEC is added to patients on stable background therapy with FF/VI.

### 6.1 Indication

Maintenance treatment of airflow obstruction

#### 6.1.1 Methods

The efficacy from studies 109 and study 110 were previously reviewed under NDA 205382 supplement 002. The previously reviewed data from both trials are summarized below for the ease of the reader.

#### 6.1.2 Demographics

In study 109 the baseline demographics were generally similar across treatment groups. The mean age was 64, 66% were male and 98% were Caucasian. The mean percent predicted pre-bronchodilator FEV<sub>1</sub> was 45%. A total of 40% of subjects had GOLD stage 2 disease, 46% had GOLD stage 3 disease and 14% had GOLD stage 4 disease. A total of 28% demonstrated reversibility to salbutamol and 50% demonstrated reversibility when salbutamol was given with ipratropium. The majority of subjects had not had an exacerbation requiring systemic steroids and/or antibiotics in the prior year (84-85%). However, all subjects had to be symptomatic to be eligible for the study (defined by an mMRC > 2) and the majority of subjects were receiving COPD treatment prior to enrolment. A total of 63% had used an ICS prior to enrollment (most commonly in combination with a LABA), 61% had used a LABA, and 21% had used a LAMA.

In study 110 baseline demographics were generally similar across treatment groups. The mean age was 63, 63% were male and 86% were Caucasian. The mean percent predicted pre-bronchodilator FEV<sub>1</sub> was 47% with 48% of subjects having GOLD stage 2 disease, 41% with GOLD stage 3 disease and 11% with stage 4 disease. A total of 29% demonstrated reversibility to salbutamol and 49% demonstrated reversibility when salbutamol was given with ipratropium. The majority of subjects had not had an exacerbation requiring systemic steroids and/or antibiotics in the prior year (86-87%).

However, all subjects had to be symptomatic to be eligible for the study (defined by a mMRC > 2) and the majority of subjects were receiving COPD treatment prior to enrolment. A total of 46% had used an ICS prior to enrolment (most commonly in combination with a LABA), 62% had used a LABA, and 46% had used a LAMA.

### 6.1.3 Subject Disposition

Study 109 included 619 randomized subjects in the ITT population, of which 206 received placebo + FF/VI, 206 received UMEC 62.5 + FF/VI and 207 received UMEC 125 + FF/VI. The overall early withdrawal rate for the study was 7% with similar rates seen across treatment groups (placebo 7%; UMEC 62.5: 5%; UMEC 125: 9%). Similar rates across groups were also seen for discontinuations due to adverse events (<1-2%), lack of efficacy (2-4%) and COPD exacerbation (2-4%). The mean treatment compliance was high throughout the study. Compliance with the open-label FF/VI Ellipta was > 98% both during run-in and during the double-blind treatment period, and compliance with UMEC Ellipta or placebo during the double-blind treatment period was 99%.

Study 110 included 619 subjects in the ITT population, of which 206 received placebo + FF/VI, 206 received UMEC 62.5 + FF/VI and 207 received UMEC 125 + FF/VI. The overall early withdrawal rate for the study was 7%, (placebo 13%; UMEC 62.5: 5%; UMEC 125: 3%). The higher early withdrawal rate in the placebo + FF/VI treated subjects is suggestive of added benefit provided by UMEC to FF/VI treatment. Similar rates across groups were seen for discontinuations due to adverse events (<1-4%), lack of efficacy (1-5%) and COPD exacerbation (1-5%). For each of these, the highest rates were seen in placebo + FF/VI subjects. The mean treatment compliance was high throughout the treatment period. Compliance with open-label FF/VI Ellipta and double-blind treatment was > 98% both during run-in and during the double-blind treatment period, and compliance with UMEC Ellipta or placebo Ellipta during the double-blind treatment period was >98%.

### 6.1.4 Analysis of Primary Endpoint(s)

Statistically significant and clinically meaningful improvements in the mean change from baseline in trough FEV<sub>1</sub> were demonstrated for both doses of UMEC compared to placebo (background FF/VI only) in both studies. No incremental treatment benefit is provided by the higher UMEC 125 dose over the UMEC 62.5 dose (Table 5). The 62.5 dose of UMEC is dose approved for treatment of COPD in the United States.

**Table 5: Difference from Placebo for change from baseline in trough FEV<sub>1</sub> and WM FEV<sub>1(0-6hr)</sub>**

	UMEC 62.5 + FF/VI	UMEC 125 + FF/VI
<b>200109</b>		
Day 85 Trough FEV <sub>1</sub>	0.124	0.128
95% CI	0.093, 0.154	0.098, 0.159
p-value	<0.001	<0.001
Day 84 WM FEV <sub>1(0-6h)</sub>	0.153	0.140
95% CI	0.118, 0.187	0.106, 0.175
p-value	<0.001	<0.001
<b>200110</b>		
Day 85 Trough FEV <sub>1</sub>	0.122	0.111
95% CI	0.091, 0.152	0.081, 0.141
p-value	<0.001	<0.001
Day 84 WM FEV <sub>1(0-6h)</sub>	0.147	0.135
95% CI	0.114, 0.179	0.103, 0.167
p-value	<0.001	<0.001

Source: Table 10 of Statistical Review for NDA 205382 supplement 2 by Dr. Yi Ren dated February 2, 2016

### 6.1.5 Analysis of Secondary Endpoints(s)

The change from baseline in WM FEV<sub>1</sub> data are also summarized in Table 5. Similar to the primary endpoint, statistically significant and clinically meaningful improvements are seen for both UMEC treatment arms compared to placebo. No incremental increase in the treatment arms are seen for the higher UMEC dose.

### 6.1.6 Analysis of Secondary Endpoints(s)

SGRQ-C was measured as an additional endpoint in both studies. In Study 110, a day 84 responder analysis, where responder is defined by a reduction from baseline of 4 units, demonstrates an increase in the number of responders in the UMEC 62.5 + FF/VI treatment arm compared to the FF/VI (35% vs 21%; odds ratio 2.0 95%CI [1.3, 3.1]). In Study 109 the UMEC 62.5 + FF/VI treatment arm had 40% responders compared with 35% in the FF/VI arm providing for an odds ratio of 1.2 with a 95% CI of 0.8 to 1.8.

In Study 109, subjects receiving UMEC + FF/VI had a greater percentage of rescue-free days over Week 1-12 than those treated with FF/VI alone (placebo + FF/VI: 3.8%; UMEC 62.5 + FF/VI: 14.2%; UMEC 125 + FF/VI: 8.7%). In Study 110 subjects receiving UMEC + FF/VI had a greater percentage of rescue-free days over Week 1-12 than those treated with FF/VI alone, although the effect size was more limited than that seen in study 109 (placebo + FF/VI: 2.3%; UMEC 62.5 + FF/VI: 6.9%; UMEC 125 + FF/VI: 5.9%).

Subjects in the UMEC treated group also had a faster median time to onset on Day 1 of treatment (placebo + FF/VI: 180 minutes; UMEC 62.5 + FF/VI: 30 minutes; UMEC 125 + FF/VI: 30 minutes). Umeclidinium added to FF/VI provided for improvement in change from baseline in peak FEV<sub>1</sub> at Day 1, 28, and 84 as well. In study 110, subjects in the UMEC treated group also had a faster median time to onset on Day 1 of treatment (placebo + FF/VI: 182 minutes; UMEC 62.5 + FF/VI: 30 minutes; UMEC 125 + FF/VI: 30 minutes). UMEC added to FF/VI provided for improvement in change from baseline in peak FEV<sub>1</sub> at Day 1, 28, and 84 as well.

### 6.1.7 Subpopulations

The pooled subpopulation data from Studies 109 and 110 do not demonstrate any clinically significant differences.

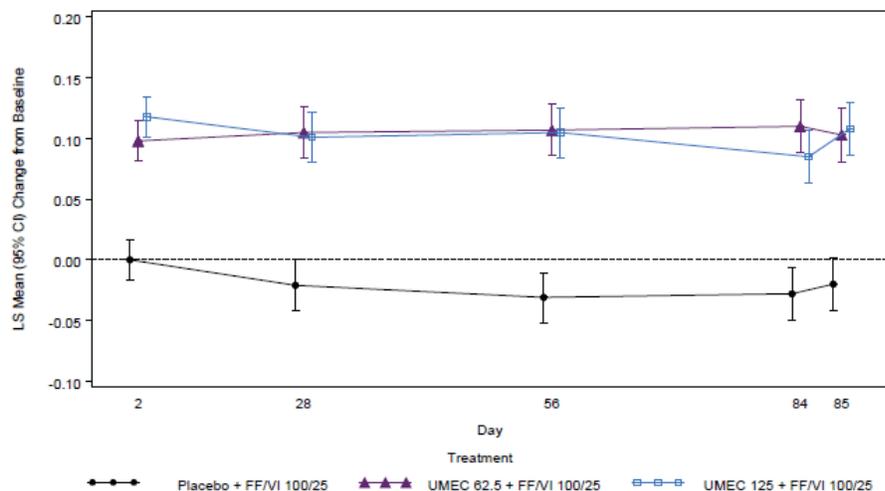
### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The data from studies 109 and 110 support the inclusion of the approved dose of UMEC (62.5) into the fixed-dose triple combination product.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The FEV<sub>1</sub> over time data demonstrate a sustained treatment effect on FEV<sub>1</sub> throughout dosing. A representative figure from Study 109 is presented below.

**Figure 4: LS mean change from baseline in trough FEV<sub>1</sub>; 200109 ITT population**



Source: NDA 205382 supplement 002 CSR 200109 Figure 2

## **7 Review of Safety**

### **Safety Summary**

In addition to the safety data provided by studies 109 and 110, the safety of FF/UMEC/VI is informed by the large safety databases for FF/VI, UMEC/VI and UMEC in COPD. No new safety signals have been identified from a review of the data from studies 109 and 110.

### **7.1 Methods**

#### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

As discussed earlier data from studies 109 and 110 were previously reviewed for NDA 205382 supplement 002. Summary findings of the safety data from these studies are presented below.

#### **7.1.2 Categorization of Adverse Events**

In both studies 109 and 110, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subjects, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product. The AEs were coded and group using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 for the pooled databases for FF/VI while the complete study reports for studies 109 and 110 were coded using MedDRA version 16.1.

#### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

This review presents data from the pooled analyses of studies 109 and 110.

### **7.2 Adequacy of Safety Assessments**

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 826 subjects received 12-weeks of therapy with UMEC + FF/VI. As discussed above, all three components are approved for use in the United States with well characterized safety profiles and routinely used in combination in patients with severe COPD. As such, the safety database from these two studies is adequate to support approval of the fixed-dose, triple combination product.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile for these components in FF/VI/UMEC are well characterized in COPD. Cardiovascular safety, pneumonia and LRTIs were prospectively assessed in each of the studies. The sponsor used a combination of MedDRA SMQs or high level terms (HLTs) to evaluate these events. If these were not available, investigator-determined grouping of Preferred Terms was used. These groupings were reviewed by this reviewer during review of the NDA 205382 supplement 002 and found to be reasonable.

## 7.3 Major Safety Results

### 7.3.1 Deaths

A total of six deaths were reported in studies 109 and 110 with five occurring in the placebo group (background FF/VI only) and one in UMEC + FF/VI treatment group. Deaths are not unexpected in a COPD population and no safety concerns are raised for use of the three products in combination from review of the individual cases or the aggregate data.

**Table 6: Summary of Deaths from Studies 109 and 110**

Treatment	Study	Age/ Sex	Notes
Placebo + FF/VI	109	66/M	Acute cardio-respiratory arrest on Day 4 of the study
Placebo + FF/VI	110	61/F	Myocardial infarction 87 days after start of FF/VI and 59 days after start of placebo + FF/VI. Treatment was discontinued and subject expired.
Placebo + FF/VI	110	45/M	Myocardial infarction 70 days after start of FF/VI and 42 days after start of placebo + FF/VI. Subject expired the same day as the MI.
Placebo + FF/VI	110	59/F	Myocardial infarction 41 days after start of FF/VI and 12 days after placebo + FF/VI. Subject expired the same day as the MI.

Treatment	Study	Age/ Sex	Notes
Placebo + FF/VI	110	75/M	Pneumonia 92 days after start of FF/VI and 67 days after start of placebo + FF/VI. Subject died the same day as the pneumonia.
UMEC 62.5 + FF/VI	110	66/M	Gastric ulcer 30 days after starting FF/VI and 2 days after starting UMEC + FF/VI. Six days after hospitalization, subject developed an MI, cardiogenic shock and severe atrial fibrillation

Source: NDA 205382 supplement 002 Summary of Clinical Safety pages 50 – 53.

### 7.3.2 Nonfatal Serious Adverse Events

No new safety signals are seen from a review of the non-fatal SAE data. The frequency of non-fatal SAEs was similar across treatment arms (2%-3%). The most commonly reported SAE was COPD, which is not unexpected in a COPD development program. The highest incidence was seen in the UMEC 125 + FF/VI treatment arm (1%) compared to < 1% in the UMEC 62.5 + FF/VI and FF/VI + placebo treatment arms. No other non-fatal SAE was reported with an incidence > 1% in any treatment group.

### 7.3.3 Dropouts and/or Discontinuations

Overall completion rates for the studies was high, with a greater number of subjects withdrawing from the placebo + background FF/VI arm than UMEC + FF/VI arms.

	Placebo + FF/VI N = 412	UMEC 62.5 + FF/VI N = 412	UMEC 125 + FF/VI N = 414	Total N = 1238
<b>Completion Status, n (%)</b>				
Completed	371 (90)	390 (95)	389 (94)	1150 (93)
Withdrawn	41 (10)	22 (5)	25 (6)	88 (7)
<b>Reason for Withdrawal, n (%)</b>				
Adverse event	14 (3)	9 (2)	6 (1)	29 (2)
Lack of efficacy	16 (4)	7 (2)	13 (3)	36 (3)
Exacerbation	16 (4)	6 (1)	12 (3)	34 (3)
Protocol Deviation	1 (<1)	2 (<1)	0	3 (<1)
Stopping criteria	0	0	1 (<1)	1 (<1)
Lost to follow up	2 (<1)	1 (<1)	1 (<1)	4 (<1)
Withdrew consent	8 (2)	3 (<1)	4 (<1)	15 (1)

Source: NDA 205382 supplement 002 Summary of Clinical Safety Table 10

### 7.3.5 Submission Specific Primary Safety Concerns

#### *Cardiovascular Safety*

The cardiovascular safety data from studies 109 and 110 are not suggestive of any increased risk of cardiovascular events when UMEC is added to open-label FF/VI.

**Table 7: Cardiovascular Safety Data: Studies 109 and 110**

	<b>Placebo + FF/VI N = 412</b>	<b>UMEC 62.5 + FF/VI N = 412</b>	<b>UMEC 125 + FF/VI N = 414</b>
Any event	17 (4)	9 (2)	8 (2)
Stroke	1 (<1)	1 (<1)	0
Cardiac arrhythmia	5 (1)	2 (<1)	3 (<1)
Cardiac failure	3 (<1)	4 (<1)	3 (<1)
Cardiac ischemia	4 (<1)	3 (<1)	0
Hypertension	6 (1)	2 (<1)	2 (<1)

Source: NDA 205382 supplement 002 Summary of Clinical Safety Table 45

#### *Pneumonia and Lower Respiratory Tract Infections (LRTI)*

The pneumonia and LTRI data are not suggestive of any increased risk of pneumonia or LRTI when UMEC is added to open-label FF/VI. Rather the data trend in support of a lower risk of respiratory infections when a LAMA is added to background FF/VI although no firm conclusions can be drawn given the limited nature of the data.

**Table 8: Pneumonia and LRTI: Studies 109 and 110**

	<b>Placebo + FF/VI N = 412</b>	<b>UMEC 62.5 + FF/VI N = 412</b>	<b>UMEC 125 + FF/VI N = 414</b>
Pneumonia	11 (1)	6 (<1)	11 (1)
LRTI excluding pneumonia	5 (<1)	3 (<1)	3 (<1)

Source: NDA 205382 supplement 002 Summary of Clinical Safety Table 48

## **7.4 Supportive Safety Results**

### 7.4.1 Common Adverse Events

The common AE data from studies 109 and 110 do not reveal any major differences from the expected common AEs for use of these three classes of products. The common AEs occurring more frequently in the UMEC + FF/VI treatment arms compared to FF/VI are provided in Table 9.

**Table 9: On-treatment AE reported by ≥ 1% of subjects on UMEC + FF/VI with an incidence greater than placebo + FF/VI:**

	<b>Placebo + FF/VI N = 412</b>	<b>UMEC 62.5 + FF/VI N = 412</b>	<b>UMEC 125 + FF/VI N = 414</b>
Headache	11 (3)	17 (4)	13 (3)
Back pain	7 (2)	15 (4)	7 (2)
URTI	9 (2)	10 (2)	8 (2)
Cough	2 (<1)	6 (1)	10 (2)
Dysgeusia	4 (<1)	7 (2)	6 (1)
Diarrhea	3 (<1)	10 (2)	3 (<1)
Oropharyngeal pain	0	5 (1)	5 (1)
Gastroenteritis	0	6 (1)	1 (<1)

URTI = upper respiratory tract infection

Source: NDA 205382 supplement 002 Summary of Clinical Safety Table 37

#### 7.4.2 Laboratory Findings

There were no routine hematology or chemistry assessments conducted in studies 109 or 110. This is reasonable given the approved product status for UMEC, FF/VI.

#### 7.4.3 Vital Signs

No new safety concerns were raised from a review of the pulse, systolic blood pressure or diastolic blood pressure data during prior review of data from studies 109 and 110 (data not shown).

#### 7.4.4 Electrocardiograms (ECGs)

The impact of UMEC + VI on cardiac rhythm in patients with COPD was previously evaluated during the UMEC/VI development program. The data demonstrated no clinically meaningful effects on cardiac rhythm when the two drugs were used in combination (readers are referred to the clinical review by Dr. Jennifer Rodriguez Pippins to NDA 203975 dated August 15, 2013 and the UMEC/VI product label for additional information).

### 7.6 Additional Safety Evaluations

#### 7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in either Study 109 or 110. This is not unexpected in a COPD trial.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose or drug abuse potential is anticipated with use of FF/UMEC/VI.

## 8 Postmarket Experience

As discussed earlier each component in FF/UMEC/VI is approved either as a single entity or as a component in a dual combination product for the treatment of COPD. The known safety concerns for each class of these products are discussed throughout this review.

## **9 Appendices**

### **9.1 Literature Review/References**

Literature citations are cited throughout the review as footnotes.

### **9.2 Labeling Recommendations**

This review recommends the approval of FF/UMEC/VI with a restricted indication statement that limits the indication to patients who require additional bronchodilator benefit beyond that provided by FF/VI therapy.

### **9.3 Advisory Committee Meeting**

No advisory committee meeting was held for this application.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOFIA S CHAUDHRY  
08/14/2017

LYDIA I GILBERT MCCLAIN  
08/14/2017

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 209482**

**Applicant: GlaxoSmithKline Stamp Date: November 18, 2016**

**Drug Name: fluticasone  
furoate/vilanterol/umeclidinium**

**NDA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	No new clinical data
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	No new clinical data
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)				
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number:			X	Fixed dose combination includes approved doses of each component
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	No new clinical data
18.	Do all pivotal efficacy studies appear to be adequate and			X	

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	No new clinical data
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No new clinical data
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	No new clinical data
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	No new clinical data
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Updated postmarketing data for the individual approved components provided
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	No new clinical data
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	No new clinical data
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	No new clinical data
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	No new clinical data
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver request submitted. This is appropriate for a COPD product.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No new clinical data
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	No new clinical data
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No new clinical data
37.	Are all datasets to support the critical safety analyses available and complete?			X	No new clinical data
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No new clinical data
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No new clinical data
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No new clinical data
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?			X	No new clinical data
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No new clinical data

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?   Yes**

\_\_\_\_\_  
 Reviewing Medical Officer

\_\_\_\_\_  
 Date

\_\_\_\_\_  
 Clinical Team Leader

\_\_\_\_\_  
 Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOFIA S CHAUDHRY  
01/06/2017

BADRUL A CHOWDHURY  
01/06/2017