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Respiratory Drafting Group, CHMP

Overview of comments received on ' Guideline on Clinical Investigation of Medicinal Products in the Treatment of Chronic Obstructive Pulmonary Disease (COPD) '

(EMA/CHMP/483572/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	The Netherland, Medicines Evaluation Board
2	Italy, AIFA
3	IR, IMB
4	UK, MHRA/CDRR&A EAG
5	Nycomed GmbH, Germany
6	Amgen
7	Mundipharma Research Ltd
8	Pfizer
9	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)
10	EFPIA (Contact person: Elisa Siviglia – elisasiviglia@efpia.org)
11	Global Initiative for Chronic Obstructive Lung Disease (GOLD).
12	Gilead Sciences International Limited
13	F. Hoffmann-La Roche Ltd.

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
7	We welcome the increased level of information, however the existing Guideline CPMP/EWP/562/98 is significantly extended to 16 pages without any substantively new guidance being presented to an applicant (for example regarding clinically relevant symptom scores).	Guideline deeply revised, in particular on primary endpoints to be used on confirmatory trials.
7	Given the common use of fixed combination products in COPD the legal basis should also include reference to CHMP/EWP/240/95 Rev.1. Consideration should therefore be given to how to approach new fixed combination products, for example conceding that where existing proven therapies exist, dose finding studies and drug interaction studies could be omitted.	This is addressed in a specific guideline on FDC.
9	The EFA welcomes the revision of the guideline and the opportunity to comment. We therefore would like to congratulate the EMA for taking this initiative and for a comprehensive guideline. The EFA response is solely from patient perspective, reflecting our membership composed of national COPD (and allergy and asthma) patient associations. We would also like to acknowledge the advice received from Kaisa Immonen Charalambous from EPF. The emphasis given in the proposed guideline on patient related instruments such as patient reported outcomes PROs is a huge step forward and reflects the overall positive development by the Agency to take into account the patients' perspective and further involve patients and patient representatives as equal partners alongside with scientists, national competent authorities and healthcare professional organisations. We would welcome the guidance to include the recommendation to include patient/patient representative/s into design of the study. This may help in important strategic decisions that may have significant	This is a scientific guideline intended to give advice on the methodological requirements for the clinical trials conducted during the clinical development of drugs in COPD. The contribution of patient´s is always desirable, but it is not the remit of the guideline but should be left to the sponsor´s decision.

	consequences in the future use of the treatment under investigation if approved. All international guidelines recognise the importance of implementing patient education and accessible and understandable patient information as important part of treatment although not always indicating details. There is no reference into this in this guideline. While standardising such measures may pose a challenge in a multicentre trial, not implementing it does not reflect real-life situations (how it should be in real life) and not attempting to do so may have impact in the results as some degree of patient education and information will anyway take place. We recognise that this concern may be addressed partly by clinical trials legislation but are concerned that maybe not adequately. For the future similar consultations, we propose exploring the possibility to publish a lay-friendly summary of the proposed draft document that would enable patients, carers, voluntary associations and other interested members of the public to contribute by commenting. Some of our members sent the guideline to their active volunteer patients/carers for comments, but none were received no doubt because of the very scientific nature of the document. In any case after the guideline is completed, a lay version of the document would be very welcome so that people with COPD and their carers know what sort of guidance is given for the investigation on medicines that concern them.	
10	EFPIA welcomes the revision and the opportunity to comment on the Draft Guideline on clinical investigation of medicinal products in the treatment of COPD. However, we have identified some key issues which should be addressed further in the proposed revised guideline, and a few additional topics which will have a major impact on drug development and the ability to bring new, effective, safe and accessible medicines to COPD patients worldwide and, more specifically, within the EU. **1. Reversibility of chronic airflow limitation (lines 157-162)** Current COPD guideline recommendations no longer consider the	The wording on reversibility has been revised taking on board comments received, new updated GOLD recommendation and

	degree of reversibility of airflow limitation for the diagnosis of COPD (NICE COPD guideline - 2010 update; http://www.nice.org.uk/nicemedia/live/13029/49425/49425.pdf, p 77ff) or for predicting the response to long-term treatment with bronchodilators or glucocorticosteroids (GOLD COPD guideline version 2009, www.goldcopd.com; page 6; NICE COPD (2010) guideline) This development should also be reflected in the EMA guideline and the respective passage should be revised (see proposal, Line 157-162).	discussion with experts in the field.
	2. Formal stratification (line 194) Stratifying a design by important predictors of outcome can be helpful in terms of ensuring balance, however it is not essential for data analysis. In large trials, randomisation will result in similar proportions of patients in each treatment arm distributed according to smoking status. Indeed, the standard textbook on clinical trials, *Clinical Trials: a Practical Approach*, states: "if the trial is very large, say several hundred patients […] then stratification has little point" 4. Pocock SJ. Clinical Trials: a Practical Approach. Chichester, Wiley, 1983; p. 81. Alternatives (e.g. pre-specification, post-hoc analysis) should be considered. It is thus recommended that the requirement for formal stratification be removed prior to randomisation (see proposal l 194-196).	Accepted. Text revised accordingly.
	3. Efficacy primary endpoints (lines 220-233) EFPIA considers this requirement very critical. Despite regulatory precedence where endpoints other than a composite including FEV_1 (e.g. SAWP agreed exacerbation as primary endpoint with FEV_1 as a key secondary endpoint) are concerned, the revised draft guideline continues to recommend that COPD trials include co-primary endpoints of lung function measurements, such as FEV_1 combined with clinically-/patient -relevant outcomes . We would strongly recommend alignment with previous SAWP recommendations, i.e. co-primary endpoints of lung function and symptomatic measures should not usually be required and consideration of clinically- and patient relevant endpoints beyond FEV1 (such as health status or exacerbations) should suffice to prove efficacy for both bronchodilator and non-bronchodilator agents in the context of COPD.	Accepted. Text revised accordingly to consider other possibilities.
	1. Spirometry (line 238) The sentence stating that "Spirometry should be undertaken by trained physicians according to standardised methods" is misleading. High-quality spirometry can also be reliably performed by well-trained	Accepted. Text revised accordingly.

	technicians and should not be restricted to trained physicians. This particular request is of high clinical and practical relevance and should not be confused with the physician's responsibility to assess spirometric findings. We therefore suggest replacing the term "spirometry undertaken by trained physicians" with "trained health-care professionals". This wording is also consistent with current international COPD guidelines (NICE 2010, GOLD 2009) and corresponds to normal usual clinical practice in many European countries. **2. Data following cessation of therapy (lines 582-584)** EFPIA considers this requirement to be very critical as there are currently insufficient data to make firm recommendations about the collection of data after withdrawal of therapy. Collection of data after cessation of therapy (e.g. randomised withdrawal of test product vs placebo) is quite complex with as yet unestablished methodologies and is subject to numerous co-variates. In addition, such requirements should be aligned with other major regulatory bodies' in order to facilitate the implementation of global clinical trials and global development. It is recommended that the requirement for the collection of data after cessation of therapy be omitted. Further details are provided within the following specific comments.	Accepted. Text deleted.
11	In several places in this document there is reference to the GOLD document on diagnosis and management of COPD. This document was originally launched in 2001 with annual updates and a revision every 5 years. Most references today are to the 2006 revision and its subsequent annual updates. The GOLD Scientific Committee is currently working on the 2011 revision and in a number of areas this will change aspects on severity grading of COPD and the approach to management of this disease. In the 2011 revision we will abandon the concept of staging based on FEV1 as this is clearly too simplistic. We will maintain a spirometric classification based on the same (arbitrary) cut-points as previously used for	The recommendations of the updated GOLD guideline have been considered in the final version. A discussion with representatives was held by the RDG.

	staging; however, less emphasis will be put on FEV1 for severity grading purposes. This is also reflected in the medical treatment of COPD, which will be driven mainly by symptom intensity and future risk (particularly of exacerbation). Thus, the treatment paradigm will change; this is somewhat in line with the changes to the NICE guideline on COPD from 2010. *Proposal: We would hope to get into a dialogue with EMA.* *We have not finished our writing; however, we are meeting in Modena in the first part of March to have our final discussions on the management section and it may be possible to submit parts of the draft* *GOLD 2011 document later this spring, should EMA be interested.* *Given the changes introduced in this revision we would find it slightly awkward if the revised EMA guidance was based on an outdated global document on diagnosis and management of COPD.*	
12	We have no major comments and generally agree with the proposed guidance. We do however recommend that the EMA provide specific guidance regarding the design of clinical studies to evaluate the role of anti-infectives as prophylactic or maintenance therapy in COPD.	Not accepted. Prophylactic antibiotic treatment in stable COPD is a new concept for which the experience is too limited so as to provide general valid recommendations.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
83	1	Comment: there is no evidence that early detection improves survival Proposed change: delete "prolong survival"	Accepted
87-88	1	Comment: this phrase regarding the treatment of asthma is redundant. The guideline concerns only COPD. Proposed change: to delete the phrase on line 87-88	Accepted. Text modified accordingly
89	1	Comment: one of the most important aspects of management of COPD… Proposed change: The most important evidence based treatment of COPD is the avoidance of and cessation of tobacco smoking	Accepted. The sentence has been rephrased as follows: *The most important step in treating COPD is to encourage smoking cessation.*
92- 94	1	Comment: the sentence is too long. Proposed change: a break after theophillyne). The sentence will be: "…theophillyne). In more severe cases …"	Accepted.
104-105	1	Comment: If is meant that the guideline does not focus on treatment of acute exacerbations it is recommended to include an additional statement Proposed change: addition of "This guideline will not focus on treatment of acute exacerbations."	Accepted.
141	1	Comment: lower limit of normal is abbreviated afterwards	Accepted.

		Proposed change: **l**ower **l**imit of **n**ormal (LLN)	
144	1	Comment: LLN is an abbreviation Proposed change: LLN needs to be included in the list of abbreviations	Accepted.
147	1	Comment: the line "Chest radiography helps in differential diagnosis" falls out of the blue. Proposed change: In order to make an connection with the foregoing text a small change is proposed: "Chest radiography can be of value in the differential diagnosis in suspected COPD."	Accepted.
157-162	1	Comment: Patients with predominantly asthma should indeed be excluded from clinical trials in COPD. These patients are considered asthma patients. However, patients with predominantly COPD with some degree of reversibility of FEV1 are considered COPD patients. Excluding this patients from the clinical trials may effect external validity although this is depending on the mode of action of the new product and the to be proposed indication. Proposed change: Patients with predominantly asthma should excluded from clinical trials in COPD. Although excluding patients with predominantly COPD with some degree of reversibility from the clinical trials may allow for an assessment of a homogeneous population this may effect external validity depending on the mode of action of the new product and the to be proposed indication. In case external validity is affected consistency of effect in the mixed population should be shown.	Accepted.

		However, if patients with different degrees of reversibility were enrolled, the consistency of the effect depending on the degree of reversibility should be shown.	
172-173	1	Comment: it seems that this phrase is accidentally copied Proposed change: removal of the phrase	Accepted.
178	1	Comment: recommendation for smoking cessation Proposed change: stringent recommendation for smoking cessation	Accepted
180	1	Comment: Therefore, clinical studies of medicinal products for the maintenance treatment of COPD should typically include patients with moderate to very severe disease. Proposed change: delete the in "the maintenance treatment of COPD"	Accepted
193 - 198	1	Comments: It is not straightforward that smoking history is by definition an important effect modifier. Since we are dealing with randomized trials (RCTs), confounding is a non-issue (but to be on the safe side potential confounders should be measured). Smoking cessation interventions can however also modify the treatment effect (and thus be effect modifiers). Proposed change: At the very least the word SHOULD should be changed in COULD or the sentence can be deleted (line 195). In line 198 maybe confounders is proposed to change into "may be confounders and also modify the treatment effect"	Accepted. Text modified accordingly.
196	1	Comment: stratification occurs at randomisation	Accepted

		Proposed change (if any): to remove prior to randomisation	
199-200	1	Comment: "The possibility of pharmacokinetic interactions...." should not be placed under patient characterictics and selection of patients Proposed change: replacement to section 4.3.1 pharmacokinetics	Accepted
202-204	1	Comment: 1) "The possible influence of other non-pharmaceutical management on pharmaceutical intervention… "should not be placed under patient characterictics and selection of patients 2) This sentence has multiple implications. One cannot expect that all these interactions with non-pharmacological interventions are investigated. Proposed change: 1) replacement to section 4.3.2 starting at line 568 concomitant therapy. 2) it should be more specific and just stated what should be done and what should not be done.	Accepted
206-207	1	Comment: "Medications that are permitted during the trials …" should not be placed under patient characterictics and selection of patients but under design Proposed change (if any): replacement to section 4.3.2	Accepted.

		starting at line 568 concomitant therapy	
209-211	1	Comment: "Definition of exacerbation and severity (of the exacerbation) need to be standardised… " should not be placed under patient characterictics and selection of patients Proposed change (if any): removal since it is discussed under section 4.3 which is the proper place.	Accepted
222	1	Comment: "…. one or more of the following …." Is not correct. Only improvement of airflow obstruction is not a goal of treatment. The goal is to improve symptoms e.g. dyspnoea due to airway obstruction. Improvement of airflow obstruction is only the mode of action.	Accepted. The sentence has been modified accordingly
229	1	It is proposed to add an additional sentence concerning hospitalisation and mortality. Please refer to comments line 310.	It is mentioned in the guideline.
244-245, 261-265	1	Comment: "If FEV1 is the primary endpoint, the pre-bronchodilator FEV1 is the preferred measure." However, whether the preferred FEV1 is the pre-bronchodilator FEV1 or the post-bronchodilator FEV1 or other lung function parameters (line 262) depends on the mode of action of the new drug. Proposed change: If FEV1 is the primary endpoint, the pre-bronchodilator FEV1 is the preferred measure in the development of a new product for maintenance treatment, although depending on the mode of action other lung function parameters (e.g. postbronchodilator) FEV1 could be the parameter of choice. Whether the preferred parameter is the pre-bronchodilator FEV1 or the post-bronchodilator FEV1 or other lungfunction parameters this should be justified.	Accepted. Text revised.

307	1	Comment: propose to add an additional sentence Proposed change (if any): the end of an exacerbation has to be defined clearly so that a difference between the a long existing exacerbation and a new execerbation can be measured.	Accepted. Text revised.
310	1	Comment: in view of the poor prognosis of COPD and the predicted further increasing importance of COPD as one of the leading causes of death in the world, RCTs on drugs aimed at improving survival are required. The use of survival as a (co-) primary endpoint should be encouraged. At the very least the effect on survival should be reported. It is proposed to add an additional paragraph with heading concerning hospitalisation and mortality.	Mortality is considered relevant as part of the safety evaluation but a priory not a requirement for the approval of a medicinal product in COPD (unless concerns were identified during assessment).
380-386	1	Comment: this text is redundant to lines 320 in which specific questionaires are mentioned under relevant efficacy endpoints Proposed change: removal of the lines	Text revised.
388-399	1	Comment: the lines lack a clear conclusion whether or not CT imaging will be accepted. Considering the radiation load and the use of CT imaging in studies is not validated it should not be proposed. The role of CT-imaging can be studied in a scientific programme. Proposed change: to remove lines 394-399 "To explore the possible role that CT imaging might have in clinical studies in COPD, its inclusion as a secondary endpoint could be considered."	Text revised.
453-463	1	Comment: some statements are double	Accepted. Text revised.

		Proposed change: avoidance of doublures	
530-531	1	Comment: with two primary endpoints there is multiplicity so the phrase "so that no multiplicity adjustment to significant levels would be indicated" is redundant Proposed change: removal of the phrase	Not Accepted, adjustment needed if a positive conclusion based simply on one of the components would be allowed. However, text has been revised.
553-556	1	Comment: with an add-on therapy a placebo comparison is needed added to the optimised background therapy Proposed change: acceptabel replaced by needed	Accepted.
562	1	Comment: acceptable = needed Proposed change: acceptable = needed	Accepted.
580	1	Comment: should be assessed = needed Proposed change: should be assessed = needed	Accepted.
597-598	1	Comment: not normally = normally not Proposed change: not normally = normally not	Accepted
Additional proposal for section 4.1	1	The most threating factor for extenal validity for safety is exclusion of patients with important comorbidity Proposed change: to include an additional statement	Accepted
Additional proposal for section 4.3.2 Concomitant therapy	1	Even a modest constant nutrient supply has a significant effect on outcome parameters. Starvation might lead to deterioration of nutritional status and influence RCT results. Proposal: both arms should be controlled for an identical nutritional status and nutrient supply during	Accepted.

		the intervention.	
Lines 75-77/79	2	**Comment**: Conditions such as cardiovascular effects, systemic inflammation, etc. are reported as effects of COPD, while it might be more appropriate to term them as associated extra-pulmonary symptoms. Co-morbidities are mentioned (line 79) but not defined in their nature and prevalence. These paragraphs should possibly be re-drafted to better distinguish among effects, extra-pulmonary symptoms and co-morbidities.	Accepted and text checked.
Lines 87-97	2	**Comment:** Triple therapy (LABA+ICS+anticholinergics) appear to be a therapeutic approach largely adopted in clinical practice (Jones PW, AJRCCM 2009;180:689-91; Welte T et al AJRCCM 2009;180:741-51). This approach should be mentioned and commented. There is no mention about PDE-4 inhibitors while roflumilast has recently been granted a MO in the indication COPD and included among COPD drugs by the recent up-date of the GOLD guidelines. Mention of PDE-4 inhibitors should be included	Accepted.
Lines 134-136	2	**Comment**: The duration of symptoms suggestive of COPD should be given, , It should be mentioned that cough, sputum and dyspnoea should be persistent or recurring to suggest the diagnosis of COPD.	Accepted.
Lines 175-181	2	**Comment:** The guidelines claim that "clinical studies of medicinal products for maintenance treatment of COPD should typically include patients with moderate to very severe disease". Excluding mild forms from some maintenance treatment might not exactly mirror the current ongoing debate in the clinical setting and in the literature.. (see Jones PW (AJRCCM 2009;180:689-91) who states that "…Further prospective studies of ICS+LABA should include a large proportion of a highly neglected group of patients, those with mild to moderate obstruction". The following wording is proposed at the end of line 181: "The inclusion of mild to moderate COPD patients might be considered in the development of medicinal products intended to be used in combination treatment early in the COPD disease	Accepted.

		process"	
Lines 213-218	2	**Comment:** We fully agree that "relevant identified sub-populations should be justified and defined a priori in the study protocol". We do not agree on limiting these sub-populations. In fact, COPD is a very heterogeneous disease which recently called a lot of interest for COPD phenotypes (Friedlander AL, COPD 2007;4:355-84; Han MLK et al, AJRCCM 2010;182:598-604; Shirtcliffe P et al, Curr Opin Pulm Med 2010; Dec 9 e-pub ahead of print) and on criteria for identifying them (Weatherall M et al, Eur Respir J 2010;36:472-74; Dima E et al, Int J COPD 2010;5:287-96). Phenotyping COPD patients entering clinical trials should be stimulated, and not limited or confined to post-hoc analysis.	Overall accepted.
Line 220-	2	**Comment:** The headings and sub-headings of this chapter (Methods to assess efficacy) should be revised. It is not clear whether "*Patients and investigator's reported outcomes*"(line 310) might be chosen as primary efficacy endpoints or should be preferably considered as secondary endpoints. This should be clarified. If the latter option is the case, a clearer headings for the paragraphs 4.2.1 and 4.2.2 should be considered. We suggest the following: 4.2.1 Relevant efficacy endpoints 4.2.1.1 Primary endpoints Lung function Exacerbations 4.2.1.2 Secondary endpoints Patient and investigators' reported outcome 4.2.2 Additional Efficacy Endpoints We also suggest to add on line 361: *"The following measures might be chosen as secondary additional endpoints:".*	Text completely revised. Accepted.
Lines 258-260	2	**Comment:** It should be stated the minimal period of time required for the assessment of the rate of decline of pulmonary function in an individual patient. It seems	It is difficult to establish a fixed period of time because the experience is very limited and will depend on the severity of

		not adequate and very generic for guidelines to state that it is "a sufficient period of time, of at least several years".	the studied population and might very much depend on individual characteristics. Anyway text checked.
Lines 310-361	2	**Comment:** The chapter on "Patients' and investigators' reported outcomes" combines subjective end-points evaluated by the patients and objective end-points recorded by the investigators. The evaluation of dyspnoea, sputum and cough as well as of PROs should deserve separate descriptions depending on methods used (questionnaires, diaries, objective evaluation by the physician, exercise tests), and should include recently developed and validated outcome measures such as CAT, EXACT, etc (Jones PW et al, Eur Respir J 2009;34:648-54; Leidy NK, Value Health 2010;8:965-75; Jones PW, Chest 2010;Nov 11 e-pub ahead of print).	Accepted, text revised.
Line 498	2	**Comment:** We understand that it is difficult to define minimal relevant differences. However, guidelines should attempt to define them, at least for primary outcomes.	Not accepted. There is no general agreement for the limits published in the literature and this will very much depend on the severity of patients, the type of drug and when it is administered (e.g. add-on, monotherapy, etc).
Line 587	2	**Comment:** See comment above (lines 258-260) "sufficient very long duration" is generic and should be defined.	Text revised.
Lines 595-637	2	**Comment:** *Safety***.** We agree that "a complete safety evaluation of any treatment for COPD requires focus on the occurrence of events of interest for either each individual component or known to occur with the particular combination of drugs". However, requirements for ICS are fully mentioned and also appear excessive (for instance, assessment of HPA axis function may be not be mandatory for inhaled ICS with long-standing use and proven absence of systemic availability. The same for immunomodulatory drugs. On the other hand, the same attention is not devoted to parameters for evaluating cardiovascular effects of LABA and anticholinergics. These should represent a major concern on the basis of data reported in asthma	Accepted. To be checked. Proposal included.

		as well as of the frequent association between COPD and cardiovascular diseases. Cardiovascular adverse events are only mentioned among other general adverse events (renal, hepatic, etc.).	
Line 633	2	**Comment:** Drug-drug interaction studies should be performed not only with drugs used for treating COPD but also for those used to treat most frequent co-morbidities (the issue of beta-blockers in association with LABA for instance….).	Accepted.
Other comments	2	Post-hoc sub-group analysis, if defined in advance in the protocol, may be very useful to stimulate hypothesis to be confirmed in ad hoc designed RCTs. For defining phenotypes it might be useful to suggest not only analysis of mean effects of the test drug, but also features of responders and non-responders. As a general comment, the strength of recommendations should be based on a defined degree of evidence. There is no grading of evidence for the statements reported in the guidelines. This appears to be in line with other EMA documents , however, the guidelines would be significantly enhanced in their value if an efficient system – such as GRADE (Guyatt GH et al, 2008;336:924-26)- is used for grading the quality of evidence and the strength of recommendations.	Comments taken on board. To be considered by the CHMP/Consistency/Coordinating group.
	3	The BODE criteria could also be mentioned in the Safety section, particularly if a company where to make any claim on mortality.	Accepted. Text revised.
Disease severity	3	It should be clarified that treatment arm should be stratified according to disease severity and number of exacerbations, as number of exacerbations is an important endpoint.	Accepted.
Line 59:	4	mucus hypersecretion [mucus is noun, mucous is	Accepted

		adjective]	
Line 60-63:	4	There is no mention [until l. 215, p.10] of chronic bronchitis (MRC definition) phenotype yet this has now been recognised as of regulatory significance eg in the licensing criteria for roflumilast.	Accepted
Line 70-71:	4	There is no mention of COPD co-morbidities [as distinct from extrapulmonary or systemic effects] which are currently very topical including osteoporosis, diabetes, hypertension, heart failure, metabolic syndrome, depression	The need to characterise the studied population according to co-morbidities is currently highlighted.
Lines 76 and 226	4	'no treatment is shown to modify the rate of decline in lung function' apart from smoking cessation (Lung Health Trial which involved multiple attendances, nicotine replacement, counselling etc)	Accepted.
Line 85	4	Inhaled steroids used in combination with LABAs [but LABAs are often used without inhaled steroids] so suggest LABAs with or without inhaled steroids concomitantly or in combination	Accepted.
Line 87	4	Supplemental therapies should probably mention immunisations	Accepted
Line 94	4	specifically exclude management of exacerbations	Text revised to clarify the scope of the guideline
Line 138:	4	Line 138: 'fibrosis due to alpha1-antitrypsin deficiency' must be very rare if it ever occurs and is confusing compared to the much more common emphysema or less common bronchiectasis [? just omit]	Partially accepted. Text revised.
Line 141-145	4	Addresses the simplest aspect of heterogeneity, mentioned again	Text revised.
Line 191-195	4	Should not the more general point be made more	It is sufficiently clear given that new guidelines do not pay

		explicit about the desirability of phenotyping of patients	attention to phenotype differences.
Line 151	4	Fig 1.2 Spirometric classification NICE document 2010 (not referenced at all) refers to stage 2 moderate as 50-79% and stage 3 severe as 30-49% and stage 4 very severe as 30-49% plus …..	Text revised with new GOLD recommendations.
Line 163	4	There is no mention of stability at baseline and inclusion in study usually not until more than 2 or 3 months after an exacerbation.	Accepted.
Line 197	4	Similarly maintainence on LTOT is usually an exclusion criterion	The guideline does not require exclusion of these patients but to stratify by this factor.
Line 201-201:	4	drug is intended ….. to improve airflow obstruction…..	Accepted.
Lines 207 and 460:	4	To be consistent with Line 279 - St Georges [rather than Saint Georges which is wrong]	Accepted.
Line 213:	4	Spirometry should be undertaken by trained physicians [almost never by physicians but by Lung function technicians or even nurses –substitute trained personnel	Accepted.
Line 214-217:	4	It is a disadvantage rather than an advantage that FEV1 can reflect restriction as well as obstruction since it is being used for the latter but FVC or VC better reflect restriction [very misleading statement in this context]	Accepted.
Line 218-224:	4	'pre and post bronchodilator,' since the latter is more	Accepted.

		reproducible. [important point not mentioned elsewhere]	
Line 233-237:	4	Not included and rarely elsewhere slow VC is preferred to FVC in some cases of severe airflow obstruction especially emphysema	Included.
Line 235:	4	kCO (which is primary measurement –multiplied by VA to obtain DLCO might merit mention0 [only excluded as not used in the US]	DLCO yet included.
Line 248:	4	'criteria for medical interventions might be subject to local differences' [spelling error]	Corrected.
Line 253:	4	'…..exacerbations that require treatment …..'	Accepted.
Line 260-261:		Should be 'number and severity of exacerbations' as well as rate (or frequency)	Accepted.
Line 263:		'a worsening of [rather than 'on'] the other'	Accepted.
Line 293:		'….. (CR10) scale and VAS: CR100 is preferred.'	Accepted.
Line 300:		'case by case' [unclear not patient by patient but 'study by study	Checked.
Line 304:		'Rescue medication' [ambiguous -carries 2 meaning as in COPD more usually now refers to 'rescue pack of antibiotics and steroids 'reliever or better beta2 agonist reliever medication is non-ambiguous]	Accepted.
Line 319-323:		Under Exercise capacity 'shuttle walk test merits mention as widely employed.	Accepted.

Line 338:		'exposure to radiation' [rather than to irradiation]	Accepted.
Line 340:		'observed changes in lung tissue are functional' is not meaningful. What is meant? That changes have functional significance? Very difficult to measure unless gross [possibly by MRI, or CT for anatomy]	Text revised. Structural changes insufficient unless followed by functional improvement.
Line 377:		'actuation of the device by inspiration (of breath) is redundant and confusing!]	Accepted.
Line 511-512:		Study duration Nowadays mortality deserves mention as an efficacy endpoint as well as safety endpoint so something about 4-5 year study duration should be included [cf Torch and Uplift]	It is currently included as a safety endpoint. Not a requirement for MAA of a new medicinal product.
Line 539:		Safety concerns - 'particular combinations of drugs'	Accepted.
Line 550:		Cardiovascular adverse effects - should not heart failure, cardiac death be specifically mentioned	Accepted. Text revised.
Line 85:		Commonly used treatments also include theophylline, and mucolytic	Text revised accordingly.
Line 137:		A high proportion of COPD patients have bronchiectasis when assessed with HRCT, although this is usually undiagnosed. I cannot see a need to exclude them if they also have COPD, and if they were really to be excluded then every subject would need a scan	Partially accepted. Text sufficiently flexible.
Line 141:		The degree of 'reversibility' (FEV1 increase after	Text deeply revised.

		maximal bronchodilatation) is not a fixed entity and has been shown to vary within individuals over time. As long as it was under 200ml then I don't think this should influence trial entry	
Line 146:	4	'Severity' can also be assessed on the basis of functional impairment, and there is only a weak relationship between physiological and functional impairment. I think the severity of impact of the disease on the individual also needs to be defined at baseline and matched between arms of a trial	Accepted.
Line 163:	4	As above, I feel that health status impairment should also be documented at baseline using a validated questionnaire. Ideally, exercise capacity, as for example a 6-minute walk test/shuttle test should also be defined	Accepted.
Line 181:	4	The most important factor here is whether or not pulmonary rehabilitation has been achieved	Sentence removed.
Line 191:	4	I'd feel that another sub-population definition could be one based on health status impairment (QOL questionnaire score)	No need to mention. It is sufficiently flexible to justify the factors selected by Applicant on a case by case basis.
Line 205:	4	Re co-primary outcomes: It's possible that a new therapy may have effects of some clinically important aspects of COPD, e.g. exercise capacity, exacerbation frequency, without having an effect of FEV1. Such a result should not be viewed as a 'negative' study. I can't see why lung function always needs to be a primary outcome- it certainly should always be measured, but there may well be interventions measured for which there is little or not a priori reason	Accepted. Text modified accordingly.

		to expect an improvement in lung function	
Line 218:		Why pre-bronchodilator FEV1? I would think post would be better, although both should be measured. Pre-bronchodilator level may be difficult to measure in long acting bronchodilators, particularly the 'ultra' long acting products under development	Accepted.
Line 278:		The CAT (COPD Assessment Test) questionnaire is very suitable for clinical trials and should be mentioned here.	Accepted.
Line 319:		I would have thought that exercise capacity could be used as a primary outcome.	Accepted. Text revised.
Line 313:		Thought should be given to combining pharmacological interventions under investigation with pulmonary rehabilitation programmes (as has been done with tiotropium previously) to allow the benefits to become apparent	Not explicitly excluded.
Line 343:		There is a strong and growing argument for composite measures such as the BODE or DOSE indexes to be used as a primary out come measure	Do not explicitly excluded this possibility.
Line 445:		I don't really understand this- if masking is not feasible how can a blinded comparison with placebo arm be included?	Not accepted. Blinded evaluation.
Line 394:		Biomarkers may be used to help define phenotypes and sub-groups, but probably not as outcome measures. There is, for instance, evidence that the COPD patients	Accepted. In COPD its role is to be established.

		with predominant eosinophilic inflammation have a better response to inhaled steroids both in terms of short and long-term outcomes	
Line 519:	UK	I don't agree that these studies are not feasible- some have already been performed- they are however costly and difficult	Accepted.
Lines 92-95	5	Comment: The mainstays of drug therapy for symptomatic relief in stable COPD in more severe disease have been amended as per recent GOLD treatment guideline update 2010 for PDE-4 inhibitors (roflumilast). Proposed change: "The mainstays of drug therapy for symptomatic relief in stable COPD are bronchodilators (...) and in more severe disease inhaled glucocorticoids and / or oral PDE-4 inhibitors used in combination with long-acting bronchodilatorsß2 agonists (LABA)".	Partially accepted.
Lines 183 to 191	5	Comment: Baseline data on concomitant diseases related to COPD such as weight loss and peripheral muscle wasting and dysfunction may be difficult to assess for each patient and may not be necessary for each clinical trial. The assessment of these parameters should be optional, depending on outcome parameters of the clinical study, and not mandatory. Proposed change: "Patient and disease characteristics at baseline (i.e., demographic data, including age, sex, body mass index, pre- and post-bronchodilator FEV1, disease reversibility, dyspnoea scale, duration of the disease, frequency, duration, severity and management of acute	Not accepted. The potential effect in these conditions is quite relevant from a clinical view point and should be addressed unless justified.

		exacerbations in the last year prior to study inclusion, previous and concomitant therapies, and, depending on study objective, concomitant diseases including those specifically related to COPD such as weight loss and peripheral muscle wasting and dysfunction) should be well documented.	
Lines 238-239	5	Comment: In the text it is stated that "Spirometry should be undertaken by trained physicians according to standardised methods." This should be rephrased, since in clinical practice, well-specially trained technicians and/or nurses may also perform this test. Proposed change: "Spirometry should be undertaken by trained ~~physicians~~ personnel (e.g. trained pulmonary technicians, nurses, or physicians) according to standardised methods.	Accepted.
Lines 338-340	5	Comment: In the text it is stated that "Alternatively; there are two common methods for patients with COPD to rate their dyspnoea during an exercise test such as cycle ergometry or treadmill walking: 0-10 category ratio (CR10) scale and VAS, CR10 is preferred". In COPD severity grade 3 and 4 according to GOLD, there is usually a moderate to high impairment of exercise capacity, accompanied with necessary addition of oxygen. Therefore, in this population cycle ergometry or treadmill is seen difficult to be performed in a clinical trial setting in contrast to the six-minute walking distance (6-MWD), which has been shown to be feasible as well as reliable in the severe population and which can be also performed under oxygen therapy. The 6-MWD is also mentioned in lines 370-378, Secondary efficacy endpoints. Proposed change: Alternatively; there are ~~two~~ common methods for patients with COPD to rate their dyspnoea during an	Text revised.

		exercise test such as cycle ergometry, ~~or~~ treadmill walking (0-10 category ratio CR10 scale and VAS, CR10 is preferred) or six-minute walking distance (6-MWD).	
line 229	6	Comment: In respiratory disease states, improvements in various lung function measurements are important endpoints, that may be clinically relevant even in the absence of improvement in other endpoints. Likewise, improvement in other endpoints, such as composite scores or functional status, may still be clinically relevant in the absence of lung function improvement. Therefore, we believe it is too constraining to require all studies to have co-primary endpoints. Proposed change (if any): remove or qualify language regarding requirement to demonstrate efficacy in co-primary endpoints.	Accepted.
line 269	6	Comment: Pre-specification of spirometry validation is usually described in an SOP from the vendor according to ATS/ERS guidelines and is not incorporated in the protocol. This is an extensive document that would unnecessarily burden the protocol. Proposed change (if any): allow protocol to cross-refer to ATS/ERS statement or to external SOP. Also, replace sentence from 269-271 with "It should be stated explicitly how valid or invalid measurements will be used in the study analysis."	Accepted.
line 358	6	Comment: questionnaires also include symptom questionnaires and may be incorporated into electronic diaries. Also, further clarification of the definitions and clinical differences between mild and moderate-severe exacerbations should be provided. The distinction	Accepted.

		between "unreported" and "reported" exacerbations seems to not apply since electronic diaries would capture both. Proposed change (if any): Add the following language "Diary entries may also be entered into an electronic diary, which may also capture symptoms in addition to exacerbation data."	
Line 525-531	6	Comment: See comment for Line 229. Lung function improvement alone may still be clinically meaningful, and symptom score improvement alone may also be clinically meaningful. Therefore, a requirement for all pivotal studies to have co-primary endpoints may set the hurdle too high for certain drugs that nevertheless can prove clinical value.. Proposed change: remove or qualify language regarding requirement to demonstrate efficacy in co-primary endpoints.	Accepted.
Line 582	6	The need for "data following cessation of therapy (eg randomised withdrawal of test product versus placebo)" is questioned in a chronic, progressive and non-reversible condition such as COPD where drug cessation upon remission is unlikely to be part of the treatment paradigm (e.g line 597 states "in COPD reduction of therapy once symptom control has been achieved is not normally possible"). Line 629 states "adequate follow-up of patients after treatment withdrawal is required to assess any possible rebound effect or any other adverse effect". Further clarification is requested on situations where prospective assessment of drug cessation is required (eg randomised withdrawal design) versus	Partially accepted. Text revised.

		follow-up of patients who voluntarily withdraw from treatment.	
Lines 407-468	7	Comment: Section 4.3.1 – it is not made clear that PK studies are recognised as being conducted in healthy subjects Proposed change (if any): NA	No changes needed. For further details, reference to the OIP guideline is made at the beginning of the guideline.
Lines 585-588	7	Comment: Under legal basis reference is made to ICH E10 (choice of control groups) however placebo controlled studies have been implied on a number of occasions, not least lines 585-588. As COPD studies of significant duration will be required and recognising that placebo controlled studies raise ethical concerns, the guideline could be clearer in advocating active controlled designs. Proposed change (if any): NA	No changes considered needed. Text however has been fully revised.
Line 536	7	Comment: The paragraph beginning line 536 appears difficult to achieve due to the clinical and ethical constraints of chronic COPD patients – all patients should receive adequate maintenance therapy whilst a 3-arm design including a placebo arm is the 'preferred option'. Proposed change (if any): NA	Text revised.
Line 100	8	Comment: Line 100 makes reference to "...guidance for the clinical evaluation of new medicinal products". The term "new medicinal products" could also be considered to relate to new products of existing active substances. We believe such products fall outside the scope of this guidance and the requirements for their development is addressed in the Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products	Accepted and changed accordingly.

		(OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and For Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 rev. 1). Proposed change (if any):Change "New Medicinal Products" to "New Active Substances".	
Line 117	8	Comment: Line 117 makes reference to the "Requirements for Clinical Documentation for Orally Inhaled Products for Use in the treatment of Asthma and COPD (CPMP/EWP/4151/00 Rev.1 and /48501/08). 1) We would suggest the use of the full title of Guideline CPMP/EWP/4151/00 Rev.1. to avoid confusion. 2) We believe reference 48501/08 refers to a draft guideline entitled "Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) Appendix 1. As this draft covered aspects of OIP development relating to Paediatrics that were modified through comment and incorporated into the adopted guideline CPMP/EWP/4151/00 Rev.1 this reference should be deleted. Proposed change (if any):	Accepted.

		1) Reference: Guideline on the requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and For Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 rev. 1). 2) Delete and /48501/08.	
134-135	8	Comment: Should this say AND a history of exposure to risk factors rather than OR? Proposed change (if any): Update if incorrect	No need for revision.
150 -162		Comment: The guideline would appear at odds with globally accepted clinical guidelines for the diagnosis of COPD with respect to the use of airflow reversibility (to short-acting bronchodilator) as a means of selecting the target population/ defining a population as suffering from COPD. For example, in the GOLD 2009 update (page 4 2nd para) it is clear that the degree of reversibility of airflow limitation is not recommended for diagnosis of COPD (including differential diagnosis vs asthma). Proposed change (if any): We would suggest that diagnosis of COPD is based on symptoms, airflow limitation after bronchodilation and risk factors (cf GOLD and other available guidelines for diagnosis of COPD) NOT on the absence or presence of a certain level of bronchodilator reversibility.	Text fully revised.

160-162	8	The guideline suggests that sponsors show consistency of effect depending on the degree of reversibility, but there is no clarification or suggestion around what criteria should be used i.e. what % reversibility would be relevant to include in stratification (9%, 12%, 15%?) or how such reversibility should be assessed in COPD patients (given that reversibility testing in COPD patients is far less reproducible over time than in an asthma population). These issues are likely to have led to the conclusion by GOLD (2009; page 4: 2nd para) that the degree of reversibility of airflow limitation is not a predictor of response to long term treatment with bronchodilators or glucocorticosteroids. Proposed change (if any): Either delete recommendation to show consistency of effect depending on degree of reversibility or include but with clarification around the assessment of and stratification for degrees of reversibility (suggestion to keep this simple, i.e. < 12 % or > 12% FEV1 increase).	Text fully revised.
184	8	Comment: 'Disease reversibility' is not a recognised clinical terminology – is this referring to airflow reversibility (based on lung function change induced by bronchodilator) as COPD is not a reversible disease? Proposed change (if any): Either amend wording to be clinically meaningful, or refer to airflow reversibility comments above and suggest delete.	Accepted.
194-196	8	Comment: It is appreciated that for putative anti-inflammatory therapies there is at least a theoretical concern that smoking status could make some classes of therapy less or indeed more effective.	Accepted.

		Whilst smoking status is an important co-variate in COPD studies it is not the only potential co-variate which could influence outcome (for example other important co-variates could include baseline lung function, exacerbation rate, sex, age, etc). Proposed change (if any): Mandatory stratification of the randomization of all COPD studies by smoking status does not seem warranted, we would suggest that smoking status is considered as a co-variate in the analysis of pivotal studies, rather than mandatory stratification.	
		There are unlikely to be many non-smokers (i.e. patients who have never smoked), in particular if studies are being conducted in the the developed world. Proposed change (if any): It is suggested that any stratification (or use of smoking status as a covariate) is based on current vs ex-smoker, not non-smokers.	To be checked.
229 (and 525-531)	8	Comment: This section states that efficacy should be demonstrated via co-primary endpoints: lung function and a symptomatic based endpoint. For demonstration of improvement of airflow obstruction for a novel bronchodilator mechanism in particular, it is proposed that a change in post dose FEV1 would be sufficient to demonstrate efficacy given the wealth of COPD bronchodilator clinical data which shows that symptomatic improvement following	Text deeply revised.

		improvement in lung function. It is therefore assumed that symptomatic endpoints need only be co-primary if a specific label claim is desired for this clinical benefit. Please clarify. In contrast, it is theoretically possible that novel anti-inflammatory therapies may have a profound effect on the rate and severity of exacerbations with little or no effect on lung function endpoints (at least acutely). It is therefore proposed that for such a therapy data supporting reduction in the rate and severity of exacerbations could support registration in the absence of lung function effects. We are concerned that the guideline specifically suggests the use of SGRQ as the symptomatic endpoint, when SGRQ has been shown to lack sensitivity to changes in health status with pharmacological therapy in COPD Proposed change (if any): With consideration of the information above please clarify, the duration and endpoints required to support different maintenance label indications for: - Improvement of airflow obstruction - symptom relief - modification or prevention of exacerbations In particular we would propose that: 1. The use of co-primary endpoints is not mandatory for all therapies, but could be justified on a case-by-case basis. 2. Other symptomatic endpoints other than SGRQ are also appropriate (eg CRQ, BDI/TDI, etc).	

238		Comment: Is this really the case that for clinical trials, the physician should be performing the lung function testing? Proposed change (if any): "Spirometry should be undertaken by trained personnel under the supervision of a responsible physician according to standardised methods"	Accepted.
251		Comment: Can the guideline be more specific on the days that post-dose FEV1 measurements would be required for multiple dose studies, e.g., just day 1 and EOT (operationally manageable) or more days.	Not accepted. To be decided on a case by case basis.
259		Comment: The "several years" should be defined, does this mean ≥3 years? Proposed change (if any):	Text checked accordingly.
330-341		Comment: It is recommended to use of patient reported outcomes to assess dyspnea but then includes the BDI/TDI as a possible choice (which is not a patient reported outcome). The outcome is confusing to sponsors, it should be stated what is acceptable to the agency and should be used to assess dyspnea as part of clinical trials. Proposed change (if any) The below proposed change assumes that all measures of dyspnea are acceptable to the agency and has been reworded accordingly.	Accepted.

		: Dyspnea should be assessed using appropriately developed and utilised PRO measurements (daily diaries and/or domains of questionnaires such as the CRQ) and/or clinician rated scales (such as the BDI/TDI).	
348-350		Comment: We acknowledge that it is difficult to define clinically relevant improvement, however, further guidance here would be useful. Proposed change (if any): Guidance on how sponsor should define improvement e.g. comparator studies, national/international treatment guidelines.	Not accepted. Specific recommendations can not be given, it should be always be defined on a case by case basis. See above.
453		It is not always possible to fully blind phase 2b studies. This is recognised on line 514 but would be useful to have in this section.	It is clearly reflected in the guideline. No need to be repetitive.
454		Comment: The aim of a dose-response study may also be to find the most effective dose. It may be to balance efficacy with safety Proposed change (if any): See above comment for consideration.	Accepted.
458		Comment: "Parallel group studies are required". Crossover studies are an option that should be seriously considered. They are ideal for chronic and stable (over the duration studied) conditions such as COPD and are more efficient in early development because they use within-subject (rather than between-subject variability) to test for significant effects. In other words, each subject is used as "their own control".	Not an acceptable option for being recommended in general terms due to the progressive course of the disease. Can be used if fully justified.

		Proposed change (if any): Please update this section with reference to the option to use crossover studies in the circumstances referenced above.	
465-468		Comment: The implied duration of a dose ranging study for non-bronchodilator mechanisms (i.e. a novel anti-inflammatory agent) is greater than 8 – 12 weeks. This seems excessive and unjustified if a dose response study is based on FEV1 or another biomarker where a shorter study should be acceptable to select an effective dose for pivotal studies. In addition for a bronchodilator mechanism, the duration of a dose ranging study stated i.e. 8 – 12 weeks is longer than has been required in order to define dose for previous molecules where studies of 4-6 weeks have been adequate. Clarification on acceptable endpoints should also be provided. Applicants should then justify the duration of the studies based on the endpoints chosen and the Mode of Action of the new drug. This paragraph suggests that for agents acting through anti-inflammatory mechanisms, i.e. non-bronchodilators that dose ranging would need to be in the exacerbation prevention studies. If a drug has an effect on FEV_1 through an anti-inflammatory mechanism can this not be used as a surrogate in order to select dose(s) for	Revised accordingly.

		phase 3? Proposed change: Provide guidance around expected length of studies and preferred endpoints with anti-inflammatory agents.	
498	8	It is interesting that the ERS/ATS taskforce document is not mentioned here for the purpose of setting decision rules (sample sizing). Would the Agency consider this?	It was considered.
Lines 514-522		Comment: This section describes the challenges that can be encountered by sponsors in fully blinding inhaled products. In these cases an unblinded control group is recognised as acceptable where effort has been made to ensure that personnel involved in the performance of efficacy tests and data collection are not aware of treatment allocation. One option, In specific cases of devices which require a capsule to be inserted into the inhaler by the patient and where it is not possible to blind the capsule itself due to markings on the capsule, we would also suggest the option of fully blinding the packaging of capsules to be used vs placebo capsules. In this way both the patient and the personnel involved in the performance of the efficacy tests will be blinded to the treatment allocation as long as a cross over study design is not used. This section should clarify if non-inferiority or superiority may be claimed in the situations described.	Not action needed. Text revised.

556		Comment: The use of ICS in COPD is still restricted to severe disease in the presence of increased frequency of exacerbations (GOLD 2009). With this considered, we the wording be "… plus ICSs where indicated. Proposed change (if any): See above.	Text revised following updated GOLD recommendations.
577		Comment: The guideline acknowledges that efficacy may be demonstrated in 12 – 24 week controlled clinical studies. It goes on to say that maintenance of effect in longer extension studies (e.g. 1 year) should be studied. It is key that the guideline is clear on the study duration requirements to demonstrate efficacy is: - improvement in airflow obstruction - symptom relief - and modifying/preventing exacerbations.	Text revised and clarified.
583	8	Comment: It should be clarified how long the randomised withdrawal period should be. How would this be considered for each drug/mechanism? On the basis of PK or PD effects? Proposed change (if any):	Done
587		Comment: The term "very long duration" should be defined. **Proposed change (if any):**	
632-634		Comment:	This should be discussed and justified on a case by case basis.

		Would it be necessary to study DDI potential in all agents e.g. tiotropium, salmeterol, formoterol, indacaterol, salbutamol, ipratropium, fluticasone propionate, budesonide etc. Would in silico modelling be an appropriate alternative? **Proposed change (if any):**	
569-570	8	"The use of all concomitant therapies should be…balanced among treatment groups". How was it envisaged that balance could be insured. Is it acceptable to do this by the randomisation or does it need to be stratified to ensure this happens. Stratification seems like an unnecessary requirement, unless the concomitant therapy is relatively common. We assume that in most cases we can rely on the randomisation.	Partially accepted. Text revised.
569		Is it necessary to stratify by background or analyse using background therapy as a covariate. This comment also links into another - there is no covariate section or recommendations of what would be considered important covariates to add to any analysis, e,g, smoking status.	Text revised.
590	Pfizer	The withdrawals advice focuses on confirmatory (Phase 3 trials), it would also be useful to have agencies thoughts on missing data within dose-response (non-confirmatory) trials.	There is a specific guideline addressing these issues.
50-58	9	Comment: Proposed change (if any): … cigarette smoking (including also second hand/passive exposure). Other	Not accepted. It is not possible to mention of noxious particles but the wording is not restricted to cigarette smoking.

		risk factors of COPD include indoor air pollution (biomass fuel used for cooking and heating*), outdoor air pollution, occupational dusts and chemicals. *highest cause in low and middle income countries Source: WHO http://www.who.int/respiratory/copd/causes/en/index.html	
79-80	9	Comment: Although this guideline is primarily intended to investigation of maintenance therapy, it is important to acknowledge that COPD cannot CURRENTLY be cured. One of the most important wishes of patients for research is finding the cure Proposed change (if any): 'COPD and its co-morbidities cannot' currently 'be cured'	It is mentioned along the guideline.
80-85	9	Comment: We very much welcome the acknowledgement of the importance of early diagnosis in the guideline	Not action needed.
89-90	9	Comment: We wonder whether this sentence also encompasses exposure to tobacco smoke, which is still unfortunately common especially in certain professions and at home. Significant exposure is important to document in a clinical study	Reflected.
183-194	9	Comment: Should significant exposure to second hand smoke and other relevant indoor pollutants be included in the documentation (even if it is not fully measurable)? See comment 1. Vaccination (seasonal flue etc) is important inclusion to the documentation.	Difficult to be accurately recorded. Not excluded.
306-308	9	Comment: External adjudication committee is mentioned here. This may not be the appropriate place, but it would be important that in such committees patient representation would add value to the diversity	To be considered by Sponsors.

		of expertise.	
310-360 380-386	9	Comment: Relevant efficacy endpoints: EFA very much welcomes the inclusion of the patients' reported outcomes, as well as those by investigators' and the general health related questionnaires as instruments. COPD is a complex disease and these instruments can bring important information regarding the treatment under investigation and capture patient related aspects that would otherwise not be documented.	No action needed.
427-437	9	Comment: The guideline recognises the need to consider patients' ability to coordinate the actuation of the inhalation device with inspiration of breath and the need to investigate the variability in performance in order to select the patient population able to use the device appropriately but does not refer to any implementation of patient education/instructing that can alter this. Proposed change (if any): We propose that the potential impact of patient education, instruction and guidance in the correct use of the device and inhalation pattern would be referred to.	The problem is highlighted.
458-463	9	Comment: We welcome the inclusion of patient reported outcomes in dose ranging studies, and hope that the intention is that patient related measures are required on recording of adverse events as well.	This is usually done.
480-483	9	Comment: We agree that the use of placebo might indeed raise ethical concerns and have even severe consequences especially in moderate to severe patients unless this is added to the best standards of care. Proposed change (if any): 'In all cases, adequate rescue measures must be implemented'. It is necessary explain more what are 'adequate' rescue measures as	No action required.

		the understanding and practise may vary significantly. For example, providing rescue medication is not sufficient on its own, but also the detailed information on rescue/support services/contact numbers etc is absolutely necessary.	
525-531	9	We welcome the recognition that lung function alone is not sufficient as only primary endpoint to patients themselves in confirmatory studies, but coupled with PROs.	No action required.
585-588	9	Comment: it is very important that the right balance between ethical concerns of a long duration placebo controlled trial and potential effect of the treatment on prevention of disease progression is struck. It is a balance between real/estimated/ documented/potential effect, respect of individual patient integrity, health and life and current and future patients who may benefit from such treatment. Proposed change (if any): Inclusion of patients/patient representatives in such considerations is fundamental.	Point taken but unfortunately it is not the correct place for this requirement.
596-625	9	Comment/Proposed change (if any): It is unclear who is indentifying and reporting safety concerns and we wonder whether patients in the study are included among key informants as they should be.	The way to record/report ADR in clinical trials is well established in EU.
634-637	9	Comment: We welcome the notion that adequate representation of patients with concomitant diseases is required as this is very common in COPD, and reflects the real-life.	NO action needed.
Line 95	10	**Comment:** The statement that in more severe disease, inhaled glucocorticoids used in combination with long-acting β2 agonists (LABA) are the mainstay of drug therapy does not reflect current COPD recommendations (GOLD 2009) that recommend inhaled glucocorticoids in addition to long-acting bronchodilator therapy.	Text revised.

		Proposed change: Inhaled glucocorticoids used in addition to long-acting ~~beta2 agonists (LABA)~~ ***bronchodilator therapy***.	
Line 99	10	**Comment:** We would appreciate it if EMA could provide some guidance on developing combination therapies, in particular on triple therapies, in the context of COPD.	Outside the scope.
Line 106-131	10	**Comment:** It is suggested to add the reference to the fixed combination guideline: CPMP/EWP/240/05 Rev.1 guideline on clinical Development of Fixed Combination Medicinal Products as most of products under development are fixed combinations.	ACCEPTED
Line 141-144	10	**Comment:** It is desirable for the guideline to reference a single FVC ratio that a Sponsor can apply globally across their programme. It is suggested that greater clarity would be achieved by referring only to an FEV1/FVC < 0.70 as this is recognised globally i.e. GOLD, NICE, joint ERS/ATS, thereby avoiding confusion.	Not acceptable. Different options are given, all generally accepted by relevant learned groups. It is clear in the guideline
Section 4.1 Line 132-218	10	**Comment:** The GOLD Document is undergoing a significant revision to be published in 2011. It is anticipated that FEV_1 will only used be used in terms of "FEV_1 Classification" and not to describe "COPD Severity", which will be described by a multi-dimensional assessment including both lung function and COPD symptoms. It is thus proposed to revisit the section after consultations with the GOLD Scientific Committee.	Accepted. Done
Line 157-162, 184	10	**Comment:** *Reversibility varies over time in COPD patients.* As acknowledged in the draft revised guideline, at least 50% of COPD patients have some degree of reversibility which represents a challenge when trying to distinguish between COPD and asthma particularly in elderly patients. In addition the NICE COPD Guideline (2010	Text revised

		update, http://www.nice.org.uk/nicemedia/live/13029/49425/49425.pdf p.77) does not recommend formal testing for the diagnosis of COPD or for predicting the response to long-term treatment with bronchodilators or glucocorticosteroids (NICE COPD Guideline - update 2010; GOLD COPD Guideline - update 2009, page 6: bronchodilator reversibility testing) . A paper that summarises the COPD NICE recommendations is also included. Avoiding such a reference is recommended when identifying and justifying the characteristics of the COPD population to be included in a clinical programme. It is thus proposed that the sentence should be deleted or alternatively, if finally patients with different degrees of reversibility are enrolled, the consistency of the effect depending on the degree of reversibility ***at randomisation*** should be shown.  O'Reilly, 2010.pdf **Proposed change:** ***At least*** ~~Up to~~ 50% of patients with COPD have some degree of reversibility***, which may vary over time***. In principle, patients who predominantly have asthma should be excluded from COPD clinical trials. ~~Although this may affect external validity, it will allow for an assessment of a homogeneous population. However, if finally patients with different degrees of reversibility are enrolled, the consistency of the effect depending on the degree of reversibility should be shown.~~	
Line 183-187 Line 295-300	10	**Comment:** **4.1. Patient characteristics and selection of patients** Frequency, duration, severity and management of acute exacerbations in the last year prior to study inclusion are listed elements of the baseline disease characteristics to be documented (Lines 183-	It is clear throughout the document.

		187). However, only frequency and severity of acute exacerbations are part of the endpoint assessment for acute exacerbation (Lines 295-300). How can duration be measured accurately in the prior year and why should it be included in the baseline assessment if it is not of importance for an endpoint assessment? In this context, it also seems important to define exacerbations to be documented, e.g exacerbations requiring systemic steroids and/or antibiotics or hospitalizations. Proposed change (if any): ....duration of the disease, frequency of exacerbations ***requiring systemic steroids or antibiotics or hospitalization***, ~~duration,~~ severity ~~and management~~ of acute exacerbations in the last year prior to study inclusion...	
Line 184	10	**Comment:** For COPD, no disease reversibility exists. Obviously, reversibility of airway obstruction is meant. **Proposed change:** ... ~~disease~~ reversibility ***of airway obstruction***..	Accepted.
Line 194-196	10	**Comment:** Stratifying a design by important predictors of outcome can be helpful in terms of ensuring balance however it is not essential for data analysis. In large trials, randomisation will result in similar proportions of patients in each treatment arm distributed according to smoking status. Whilst smoking status is an important co-variate in COPD studies it is not the only potential co-variate which could influence the outcome (other potentially important co-variates include baseline lung function, exacerbation rate, sex, age, etc). Indeed, the standard textbook on clinical trials, Clinical Trials: a Practical Approach, states: "if the trial is very large, say several hundred patients […] then stratification has little point" 4. Pocock SJ. Clinical Trials: a Practical Approach. Chichester, Wiley, 1983; p. 81. The stratification of patients according to smoking status before randomisation may not be necessary in	Accepted. Text revised.

		large studies, where a similar distribution can be expected in the different treatment arms. **Proposed change:** In efficacy studies ***evaluation could consider analyses based on smoking status. F***ormal stratification of patients according to smoking status (non-smokers, current smokers, ex-smokers) ~~should be carried out~~ ***could be considered*** prior to randomisation ***if necessary***.	
Line 199-200	10	**Comment:** The term 'investigated' needs to be specifically clarified: Routine PK evaluation of interaction with all potential replacement therapies seems excessive. *In vitro* data can reliably exclude interactions without the need for performing specific clinical interaction studies. In addition, depending on the metabolic pathway, it may or may not be necessary to investigate pharmacokinetic interactions between the new product and any replacement therapy. **Proposed change:** The possibility of pharmacokinetic interactions between the proposed new product and any replacement therapies should be ~~investigated~~ ***considered.***	Accepted.
Line 202-204	10	**Comment:** This is a complex requirement. In our opinion, it should be sufficient to specify how non-pharmacological management was handled in a trial. Sometimes, it may be a criterion for exclusion (frequently the case, for example; for regular daytime oxygen therapy, previous lung volume reduction surgery, and recent participation in a pulmonary rehabilitation programme); in other cases, it may suffice if a table with baseline demographic and other variables demonstrates that randomisation was successful with regard to these factors. **Proposed change:** The possible influence of other non-pharmaceutical management on pharmaceutical intervention, e.g	Not accepted.

		surgical treatment, oxygen, physiotherapy, exercise, etc, should be ~~investigated~~ ***considered***.	
Lines 220-233	10	**Comment:** **4.2. Methods to assess efficacy** This section states 'efficacy should be demonstrated in two endpoints (co-primary)'. It is recommended that one primary endpoint should be a lung function measurement and that the other should be some form of symptom-based assessment. Requiring co-primary endpoints with lung function and symptoms is problematic because (1) it reduces flexibility for designing relevant trials based on mechanism of action, (2) it increases the probability of negative trials because of the poor correlation between lung function and other symptom-based measures, and (3) it greatly increases the sample size compared to a trial design with a primary endpoint of lung function and a key secondary endpoint of respiratory symptoms, exacerbations, or patient-reported outcomes. The recommendation of lung function measurements as a co-primary endpoint does not take into consideration the possibility that agents with either bronchodilator or non-bronchodilator modes of action may still positively affect patient-relevant outcomes. It could be argued that a marked improvement in an established patient-relevant outcome (e.g. exacerbations, health status) should provide an adequate efficacy-related basis for approval of bronchodilators or non-bronchodilator drugs, irrespective of the effect on any lung function measurement. **Proposed change:** The selection of endpoints will depend on the objective(s) of the clinical programme/clinical study. Efficacy ***could*** ~~should~~ be demonstrated using two endpoints (co-primary **or primary and key secondary appropriately controlled for multiplicity). For therapy with either bronchodilator or non-bronchodilator drugs a single symptom-based primary endpoint (e.g. exacerbations, health**	Text revised.

		status, symptoms) should be sufficient for the demonstration of efficacy. Lung function measurement (e.g. FEV1) ~~combined with instruments that encompass symptomatic based endpoints (e.g. in moderate/severe COPD exacerbation, saint George's Respiratory Questionnaire, symptoms, etc) are recommended for the demonstration of efficacy~~ should then be one of the major secondary endpoints.	
Line 238	10	**Comment:** As already mentioned in our major comments and based on usual clinical practice and guideline recommendations (GOLD..) high-quality spirometry can also be reliably performed by well-trained technicians whereas the medical assessment of spirometric results has to be done by trained physicians. **Proposed change:** "Spirometry should be undertaken by trained ~~physicians~~ ***health-care professionals***"	Accepted. Text modified.
Line 244-245	10	**Comment:** The statement that if FEV_1 is the primary endpoint, pre-bronchodilator FEV_1 is the preferred measure contrasts with the FDA draft guidance on COPD [i], that recommends pre-bronchodilator FEV_1 for non-bronchodilators and post-dose FEV_1 for bronchodilators; this resulting in challenges with respect to global drug development programmes. This approach is alluded to in lines 248 & 249. A revised wording is thus proposed. **Proposed change:** If FEV_1 is the primary endpoint, the ***mode of action of the drug should determine if*** pre- ***and/or post***-bronchodilator FEV_1 is the preferred measure.	Text revised.
Line 255	**10**	**Comment:** In this paragraph the term "serial" should be changed to "periodical", to avoid misinterpretation of requests for serial post-dose assessments over a long period of time.	Accepted.

		Proposed change: ... may be assessed by means of ~~serial~~ ***periodical*** measurements of FEV1.....	
Lines 261-264	10	**Comment:** Statement that alternative measures of lung function, such as IC, FRC, RV/TLC, VC, DLCO should be performed because they correlate better with symptoms etc. These measures of lung function may indeed be helpful. But they have not been validated as endpoints for clinical trials. In addition, the statement that these measures may correlate better with respiratory symptoms and other measures is not supported by the published literature. Finally, the outlined measures are all secondary endpoints and therefore this section could be moved to 4.2.2. **Proposed change:** Other measures of lung function which should also be ~~recorded~~ ***considered*** to characterise...	Accepted.
Lines 285 to 289	10	**Comment:** Should the definition of severe exacerbations include emergency room visits? **Proposed change:** Severe: exacerbations that require hospitalization, ***emergency room visits*** or result in death	Not generally accepted. Not included.
Line 291	10	**Comment:** Please reword "rate of moderate to severe" **Propose change:** The rate of moderate ~~of~~ ***or*** severe exacerbation...	Accepted.
Line 295	10	**Comment:** It is strongly suggested that time to first exacerbation as the most robust exacerbation endpoint (that is less likely to be influenced by patients with multiple exacerbations) or number of patients with exacerbations also be included in this sentence as these are commonly used endpoints.	Accepted.

		Proposed change: Such measures can include reduction in the severity of exacerbation***,*** ~~or~~ reduction in the frequency of exacerbation***, time to first exacerbation or reduction in the number of patients with exacerbations***	
Line 310-326	10	**Comment:** **PROs and Quality of Life measures** In the guideline, use of PROs is supported as a co-primary endpoint including SGRQ and BDI/TDI. We are supportive of use of relevant PROs and would recommend EMA to work with FDA to ensure that PROs already developed or in development are accepted globally.	Point taken.
Line 353-354	10	**Comment:** The use of rescue medication is a soft parameter often subject to recall bias and of questionable quality as capture in patient diaries, etc. Furthermore, it could also be misleading as there may be patients who are more physically active due to an effective drug and thereforeuse less rescue medication than expected. It is suggested to amend the sentence that could be moved to Section 4.2.2. on Secondary efficacy endpoints **Proposed change:** Rescue medication – the use of rescue medication ***may reflect the effects on symptoms and can therefore be considered as an additional endpoint*** ~~is considered a relevant endpoint to assess effect on symptoms~~.	ACCEPTED.
Line 362	10	**Comment:** Although mentioned in the introduction as hallmark symptoms of COPD (lines 68-74), there are no examples in section 4.2.2 of secondary outcome methods for secondary outcomes such as body composition, physical activity (Watz H et al. Physical activity in patients with COPD. Eur Respir J 2009,	Accepted.

		33:262-272), systemic inflammation blood biomarkers etc.  ERJ 2009_WATZ_physical **Proposed change :** Physical activity or systemic inflammation blood biomarkers, though still exploratory, warrant a mention in 4.2.2 as possible secondary endpoints.	
Lines 411-417	10	**Comment:** The example of FEV1 as a pharmacodynamic outcome is not useful for anti-inflammatory compounds. We would welcome the Agency's recommendations about adequate pharmacodynamic outcomes for non-bronchodilatory compounds for short and long-term trials.	It will depend on the mechanism of action. To be decided on a case by case. Not able to make a recommendation due to limited experience.
Line 458	10	**Comment:** In addition to a parallel group design, a cross-over design should also be considered in terms of dose-finding studies (Källén A, Larsson P. Dose-response studies: How do we make them conclusive? Statist Med 1999; 18: 629-641).  Källén A, 1999.pdf **Proposed change:** Double blind, randomised, ~~parallel group,~~ placebo controlled studies ***with a parallel group or a cross-over design*** are required.	Accepted.
Line 460	10	**Comment:** **4.3.1. Early studies, Dose finding studies** The document contains minimal discussion of biomarkers in general. **Proposed change:**	Accepted.

		Should the statement beginning in Line 460 only be limited to exhaled biomarkers or could it be expanded to discuss biomarkers in general? Alternatively, the word "exhaled" could be omitted and the statement would remain valid for any potential biomarker.	
Line 465-468	10	**Comment:** The duration of a dose ranging study stated i.e. 8 – 12 weeks for long-acting bronchodilators is longer than has been required to define dose for previous drugs where studies of 4-6 weeks have been adequate for approval. We would recommend EMA to work with FDA to ensure which length of studies and preferred endpoints are accepted globally for agents with different modes of action.	Accepted.
Line 493	10	**Comment:** It is suggested that the sentence relating to the choice of comparator running from Line 493 to Line 496 is moved towards the start of the paragraph and is then followed by the examples that are given relating to potential comparators in mild/severe COPD. Also clarify that the approaches given are examples of approaches that might be adopted, particularly in light of evolving treatment guidelines e.g. in the UK NICE recommends progression from short-acting bronchodilators to either ICS/LABA or LAMA for those with an FEV_1 <50%. It is generally important to try to future-proof this guidance as far as possible against what is likely to be a rapidly evolving field over the next decade.	Accepted.
Line 498-509	10	**Comment:** It can be extremely difficult to judge what degrees of effect should be considered to be 'clinically relevant' and what will not. We do accept that there are significant problems in providing definitive guidance on what comprises 'clinical relevance' in the treatment of COPD. Nevertheless, we believe that some form of guidance on this issue would be of great value to drug developers. **Proposed change:**	Not accepted. Further detail can not be given as this is an controversial area for which no agreement exist.

		For example, it could be stated that, if an approved and recognised 'standard-of-care' active comparator is included in a study (which the guideline encourages), then the efficacy effects of the test drug will be considered to be 'clinically relevant' if these are at least as good as those of the comparator.	
Line 514-522	10	**Comment:** **Therapeutic confirmatory trials** This section should clarify whether non-inferiority or superiority may be claimed in the situations described.	To be checked.
Line 521-522	**10**	**Comment:** The recommendation for an independent adjudicating committee for main efficacy outcomes other than for mortality requires clarification. Please specify in what context (unblinded comparison, blinded comparison) an adjudication committee could be required or not. **Proposed change:** In all cases ***involving unblinded comparisons*** it is recommended that the assessment of the main efficacy and safety outcomes is carried out blind by an independent adjudicating committee.	Text clarified.
Line 533-534	10	**Comment:** **Title** Should new drugs really replace well accepted therapies? If so, then it's hard to understand why in line 546, "If only a comparison with placebo is available ..." Please clarify.	Text modified.
Line 569-573	10	**Comment:** Achieving a 'balanced use' among treatment groups is not feasible. **Proposed change:** The use of all concomitant therapies should be accurately recorded and balanced among treatment groups ***at baseline***.	Accepted.

Lines 577-580	10	**Comment:** The guideline acknowledges that efficacy may be demonstrated in 12 – 24 week controlled clinical studies. It goes on to say that maintenance of effect in longer extension studies (e.g. 1 year) should be studied. It is key that the guideline is clear on the minimum length of study requirements to demonstrate efficacy in: - improvement in airflow obstruction - symptom relief (e.g. dyspnoea) - prevention of exacerbations - and improved health status	Not accepted. It will depend on many factors, i.e. the drug, the studied population,etc.
Line 582-584	10	**Comment:** Please could you clarify the need for and purpose of data following cessation of therapy? We are not aware of any comparable requirements from other large indication areas. The collection of data after the cessation of therapy (e.g. randomised withdrawal of test product versus placebo) is subject to numerous confounders (e.g. varying wash-out times, different drug modes of action, PK/PD profiles, concomitant medication, withdrawal of consent etc). The statement that data following cessation of therapy should be provided does not include any further details regarding outcomes to be assessed or duration of observation. This may not be appropriate except in long-term studies investigating disease progression. **Proposed change:** It is suggested that the demand for collection of data after cessation of therapy should be removed.	Accepted.
Line 587	10	**Comment:** The term "very long duration" should be defined. There should be more discussion and greater clarification of the duration of clinical trials in specific subpopulations in order to facilitate the implementation of global clinical trials and global development.	Text revised.
Section 4.1 line 144	13	Comment: FEV1 to FEV6 ratio less than 0.73 can suffice for	Currently recommended in that way.

		diagnosis of COPD Proposed change (if any): FEV1 / FEV6 ratio is not appropriate for diagnosis of COPD because patients with airflow obstruction may have prolonged exhalation and FEV6 may substantively underestimate FVC. FEV1/FVC ratio should be used as the preferred measure.	
Section 4.1 line 155	13	Comment: Alpha-1 antitrypsin deficient patients should be excluded from clinical studies of COPD Proposed change (if any): Patients with Alpha-1-antitrypsin deficiency and COPD should be included in trials, as they comprise a legitimate part of the spectrum of disease. Stratification by alpha-1-antitripsin status may be appropriate in studies.	Not accepted. They are completely different populations.
Section 4.1 Lines 164-170 and Figure 1-2	13	Comment: The GOLD classification scheme should be used to classify disease severity. Proposed change (if any): The GOLD scheme is indeed widely used, but is based on expert opinion and has not been formally validated. Consequently, the GOLD scheme can only be recommended as one possibility to evaluate and stage disease severity. Alternative approaches should be allowed.	Accepted.
Section 4.1 Lines 165 -	13	Comment: Patients with predominate asthma should be excluded. Proposed change (if any): Asthma and COPD can often co-exist. If there is an adequate smoking history and evidence of irreversible airflow obstruction, patients with concomitant asthma	Text revised.

		do not necessarily require exclusion from trials.	
Section 4.2 Line 229	13	Comment: Efficacy should be measured in two endpoints (co-primary) Proposed change (if any): The choice of endpoint for COPD trials will be determined, at least in part, by the mechanism of action of the drug. Depending on the mechanism, the drug may be expected to have a greater effect on lung function or exacerbations. In COPD, the correlation between lung function impairment and respiratory symptoms, health-related quality of life, and exacerbations is low-to-moderate. Consequently, requiring co-primary endpoints with lung function and symptoms is problematic because it (1) reduces flexibility to design rational trials based on mechanism of action, (2) increases the probability of negative trials because of the poor correlation between lung function and other symptom-based measures, and (3) greatly increases the sample size compared to a trial design with a primary endpoint of lung function and a key secondary endpoint of respiratory symptoms, exacerbations, or patient-reported outcomes.	Accepted.
Section 4.2.1 Line 244 - 245	13	Comment: Pre-bronchodilator FEV1 is the preferred measure Proposed change (if any): Pre-bronchodilator spirometry is the preferred measure for asthma, but not COPD. In COPD, post-bronchodilator spirometry is the preferred endpoint especially for non-bronchodilator drugs. Studies that aim to demonstrate disease modification in COPD, that a drug decreases the rate of decline of FEV1 (i.e., the slope) should use post-bronchodilator lung function to eliminate the issue of resting airway smooth muscle tone. This is standard in the field (e.g., UPLIFT trial of tiotropium).	Accepted.
Section 4.2.1	13	Comment: No treatment has been shown to modify the long-term	Accepted. Text modified.

Line 253 - 254		decline in lung function. Proposed change (if any): It is true for current COPD medications, but is generally untrue - smoking cessation (and therefore smoking cessation products) has been documented to impact the decline in lung function. Smoking is a confounding variable in these studies; infection risk, malignancy, CV events, symptoms (i.e. cough). Smoking status is a prognostic variable that at a minimum should be stratified at randomization. The COPD guidance ought to discuss smoking status.	
Section 4.2.1 line 259	13	Comment: Duration of trial for disease modification should be 'several years' Proposed change (if any): This is quite non-specific. A more specific recommendation would be more helpful, such as 3-5 years. This can be extrapolated from the Lung Health Study and UPLIFT trials.	Accepted.
Section 4.2.1 lines 261-4	13	Comment: Statement that alternative measures of lung function, such as IC, FRC, RV/TLC,VC, DLCO should be made because they correlate better with symptoms etc. Proposed change (if any): These measures of lung function may indeed be helpful. But they have not been validated as endpoints for clinical trials. In addition, the statement that these measures may correlate better with respiratory symptoms and other measures is not strongly supported by the published literature. Recommend that these measures should be 'considered' but not required.	Accepted.
Section 4.3.2 lines 525-530	13	Comment: Lung function and symptom-based endpoints should be co-primary. Proposed change (if any): See response to Section 4.2 line 229 above	

Section 4.3.2 lines 538-542	13	Comment: Study design should be three arm: new drug, established comparator, placebo OR two arm of new drug vs. comparator Proposed change (if any): In moderate-to-severe COPD, the inclusion of a placebo arm in the setting of effective standard-of-care raises ethical concerns. Suggest that the appropriate design is to demonstrate superiority to established comparator.	It is currently stated.
Section 4.4.2 lines 627-630	13	Comment: Proposed safety database of 300-600 patients for 6 months and 100 for one year Proposed change (if any): This is less than that specified by ICH guidelines (1500 for 6 months, 100 for one year).	Accepted.

[i] **Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment – Draft November 2007**
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071575.pdf