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Pre-Authorisation Evaluation of Medicines for Human Use

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**CONCEPT PAPER ON THE NEED FOR REVISION OF THE POINTS TO CONSIDER ON
CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE CHRONIC
TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
(COPD) (CPMP/EWP/562/98)**

AGREED BY EFFICACY WORKING PARTY	January 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 February 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2009

The proposed guideline will replace NfG Reference CPMP/EWP/562/98

Comments should be provided using this [template](#) to EWPSecretariat@emea.europa.eu

KEYWORDS	<i>Chronic obstructive pulmonary disease, COPD, topical and systemic disease, severity stages, treatment, MICD, biomarkers</i>
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1. INTRODUCTION

This 'Points to Consider' (PtC) document gives advice on the **clinical** development of new chemical entities / new pharmaceutical dosage forms in the treatment of chronic obstructive pulmonary disease (COPD). An update of this guideline is considered absolutely necessary to include new scientific knowledge on the pathophysiology of the disease and treatment advances.

2. PROBLEM STATEMENT

COPD is a leading cause of morbidity and mortality worldwide, and results in an enormous economic and social burden that is both substantial and increasing. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. The knowledge on the pathophysiology of this complex condition continues to grow and our ability to offer effective treatment to those who suffer from it has been improved considerably.

The awareness, the general understanding and the medical research of COPD has been markedly increased for years. COPD is now understood as a multicomponent disease characterised by a range of pathological changes, which include mucus hypersecretion, airway narrowing and loss of alveoli in the lungs, and loss of lean body mass and cardiovascular effects at a systemic level. COPD patients are also heterogeneous in terms of their clinical presentation, disease severity and rate of disease progression. Since the relationship between spirometry and symptoms appears to be poor, measures of lung physiology alone may not adequately describe the effectiveness of therapeutic interventions in individual patients.

The major aim of treatment of COPD is the primary, secondary and tertiary prevention (cessation of tobacco use). Currently, COPD can't be cured but several medicinal products (mainly orally inhaled products) aiming at improvement of quality of life and reduction of mortality are in development or have already been approved. There are several potential types of drugs that may be developed for COPD based on whether the drug is intended to improve airflow obstruction, provide symptom relief, modify or prevent exacerbations, alter the disease progression, or modify lung structure.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The following issues should be considered when updating the guideline:

- 1.) Implementation of references to several new or updated guidelines.
- 2.) Implementation of new scientific knowledge:
 - general information;
(e.g. epidemiological and pathophysiological information, pathogenesis, specific issues);
 - reversibility test of pulmonary function in COPD patients and possible influence on outcome;
 - description of the severity stages of the disease;
 - definition of the term exacerbation and severe exacerbation (e.g. Anthonisen-definition; consensus-definition from Rodriguez-Roisin; action-based definition);
- 3.) biomarkers:
 - Discussion of possible biomarkers (e.g. SP-D; CRP; Serumamyloid (SAA), N-terminal Pro-BNP; salivary cotinin);
 - need of validation of these biomarkers;
 - biomarkers as possible surrogate endpoints;
 - importance of biomarkers especially in proof-of-concept or proof-of-action studies
- 4.) update of the requirements for pivotal study/ies:
 - possible influence of non-pharmaceutical treatment on pharmaceutical intervention trials (e.g. cessation of smoking, surgical measurements, physical action, pneumo-sport) and pharmaceutical treatment (e.g. Acetylcystein)
→ necessity of a balance among treatment groups with regard to concomitant therapy
 - standardisation of clinical trials;

- recommendation of primary endpoints depending on the stage of severity (e.g. mild-moderate diseases: FEV₁/6-MWD and SGRQ; severe diseases: number of severe exacerbations; time to the first severe exacerbation; 6-MWD; mortality; BODE-Index);
 - recommendation of secondary endpoints that also reflect the systemic complexity of the disease (parameters of BODE-Index; symptom-related parameters (cough, wheezing, dyspnoe, intake of reliever medication, awakening during night); spirometric parameters (FEV₁/FVC; FIV₁); 6-MWD in correlation to HR; number of mild and severe exacerbations, mortality; assessment of muscular status, accelerometer measurements, echocardiographic investigations etc.);
 - critical discussion of active controlled clinical trials vs. Placebo-controlled trials;
 - statement on minimal differences in several COPD parameters in clinical Studies that can be considered clinically relevant (FEV₁; 6-MWD, Dyspnoe Scores, EXAC; SGRQ, exercise);
 - duration of pivotal study: longer than 6 months studies are strongly recommended;
 - inclusion of safety requirements:
 - investigation of drug interactions (cardiac treatment, vascular treatment etc.),
 - efficacy and safety of the new product in case of renal and hepatic dysfunction;
- 5.) implementation of pharmaceutical particularities:
- need of spacer development in case of orally inhaled treatment with MDI's,
 - statement of orally inhaled treatment and flow rate dependency.

4. RECOMMENDATION

It is proposed to revise the CHMP-Guideline 'Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD)' CPMP/EWP562/98 to provide an updated EU consensual regulatory point of view on the above-mentioned issues.

5. PROPOSED TIMETABLE

It is anticipated that a draft revised CHMP guideline for external consultation will be available 6 months after adoption of the CP, and a final version within 6 months after the external consultation phase.

6. RESOURCE REQUIREMENTS FOR PREPARATION

A Rapporteur and a Co-Rapporteur should be appointed to revise these Points to Consider document. Based on the complexity of the disease, the involvement of external expert(s) should be considered.

7. IMPACT ASSESSMENT (ANTICIPATED)

The revised guideline will have a major influence on the clinical development of a wide range of potential COPD drugs.

8. INTERESTED PARTIES

The Global Initiative for Chronic Obstructive Lung Disease, and the COPD groups of following societies:

European Academy of Allergology and Clinical Immunology.

European Federation of Allergy and Airways Diseases Patients Associations.

European Respiratory Society.

International Primary Care Respiratory Group.

World Allergy Organisation.

9. REFERENCES

1. 75/318 EEC - Council Regulation No. 594/91 'Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products'.
2. Anthonisen NR *et al*: Ann Intern Med 1987; 106: 196-204: Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease.
3. Barnes PJ *et al*: Lancet 2004; 364: 985-96; Prospects for new drugs for chronic obstructive pulmonary disease.
4. Bozinovski S *et al*: Am J. Resp. Crit Care Med 2008; 177: 269-78: Serum Amyloid A is a biomarker of acute exacerbations of COPD.
5. Burge PS *et al*: BMJ 2000; 320: 1297-1303; **ISOLDE**: Inhaled Steroids in Obstructive Lung Disease in Europe 'Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe COPD' .
6. Calverley P *et al*; Lancet 2003; 361: 449-56; **TRISTAN**: Trial of Inhaled STeroids And long-acting β_2 -agonists 'Comined salmeterol and fluticasone in the treatment of COPD: a randomised controlled trial'.
7. Calverley P *et al*: NEJM 2007; 356: 775-89; **TORCH**: Towards a Revolution in COPD Health 'Salmeterol and Fluticasone Propionate and Survival an COPD'.
8. Casanova *et al*: ERJ 2007; 29:535-40; 6MWD: 6-min walking distance: long-term follow up in patients with COPD.
9. Cazzola M *et al*: Eur Respir J 2008; 34: 416-68: Outcomes for COPD pharmacological trials: from lung function to biomarkers.
10. Celli BR *et al*.; NEJM 2004; 350: 1005-12; BODE: The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease.
11. CPMP/EWP/239/95 'Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing known Constituents'.
12. CPMP/EWP/240/95rev. 'Note for Guidance on fixed Combination Medicinal Products'.
13. CPMP/EWP/4151/00rev. 'Points to Consider on the requirements for Clinical Documentation for Orally Inhaled Products'.
14. LHS Research Group; NEJM 2000; 343: 1902-9; **LHS**: Lung Health Study 'Effect of inhaled triamcinolone on the decline in pulmonary function in COPD'.
15. Marek W *et al*: Pneumologie 2008; 62: 643-54: Ein numerischer Verfahren zur Objektivierung der körperlichen Leistungsfähigkeit im Rahmen der stationären Rehabilitationsaufenthaltes mittels 6-Minuten-Gehtest.
16. Pauwels RA *et al*: NEJM 1999; 340: 1948-53; **EUROSCOP**: European Study on Chronic Obstructive Pulmonary Disease; 'Long-term effect of inhaled budesonide in mild and moderate COPD who continue smoking'.
17. Rodriguez-Roisin R; Chest 2000; 117: 398S-401S: Towards to a consensus definition of COPD exacerbations.
18. Tashkin D *et al*: NEJM 2008; 359: 1543-54; **UPDATE**: 'A 4-year trial of tiotropium in chtonic obstructive pulmonary disease'.
19. Vestbo J *et al*: Lancet 1999; 353: 1819-23; **Copenhagen City Lung Study**: 'Long-term effect of inhaled budesonide in mild and moderate COPD: a randomised controlled trial'.

10. LIST OF ABBREVIATIONS

6-MWD	6-minutes walking distance
BODE-Index	Body-mass-index / obstruction / dyspnoe / exercise capacity - INDEX
COPD	Chronic obstructive pulmonary disease
EXAC	exacerbations
FEV ₁	Forced Expiratory Volume in one second
FEV ₁ /FVC	Tiffenau-Index

FIV ₁	Forced Inspiratory Volume in one second
FVC	Forced vital capacity
HR	heart rate
MDI	Metered Dose Inhaler
SGRQ	St. George Respiratory Questionnaire