EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 March 2010
EMA/432157/2009 Corr.*

Overview of comments received on draft guideline on the development of medicinal products for the treatment of smoking (EMEA/CHMP/EWP/369963/05)

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

Stakeholder no.	Name of organisation or individual
1	Society for Research on Nicotine and Tobacco (SRNT)
2	Royal College of Physicians
3	Smoking Prevention Group of the Spanish Respiratory Society (SEPAR)
4	National Association of Women Pharmacists (UK)
5	EFPIA
6	Merck Sharp & Dohme (Europe) Inc.
7	Johnson & Johnson Consumer Group (JJCG)
8	Dr. Peter Hajek
9	Association of the European Self-Medication Industry (AESGP)
10	The Proprietary Association of Great Britain, (PAGB including Johnson & Jonson Consumer Group, GlaxoSmith Kline Consumer Healthcare and Novartis Consumer Health)

*Comments 9 and 10 have been included

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GENERAL COMMENTS – OVERVIEW:

COMMENTS FROM : Society for Research on Nicotine and Tobacco (SRNT), Europe

GENERAL COMMENTS

SRNT Europe, representing European scientists in the field of nicotine and tobacco research, is concerned that this guideline in its present form will be a barrier to the development of new effective medications for smoking cessation. Smoking is a main health burden, causing about 5 millions premature death worldwide each year. Guidelines should facilitate the emergence of new treatments in as little time as possible. We thus suggest rewriting of this guideline.

Considering WHO Europe position on the regulation of nicotine replacement therapy (http://www.euro.who.int/document/e74522.pdf), and changes that occurred consequently in the regulation of these products in France and UK, this present guideline is not representing the current evidence base about smoking cessation treatments. The consequences of such a guideline could be to deter new product development and improved use of available therapies. Members of SRNT Europe are surprised how poorly referenced this guideline is, and would have liked to have been consulted for the drafting of it. SRNT Europe is ready to provide experts to reconsider the content of this guideline.

Note: See summary of outcome at the end of the document for comments.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
L18	Definitions of dependence (DSM-IV-TR, ICD 10, etc.) when applied to tobacco are problematic because there is minimal evidence for continued escalation of use (i.e., "difficulty in controlling the level of use").	Present some cautions about these definitions. **Outcome**: *The validity of these diagnostic criteria are indeed debated. An in-depth discussion about the limitations of the DSM-IV/ICD-10 criteria is however beyond the scope of this document, as these criteria are not required anymore as diagnostic criteria in the final Note for Guidance.*
L 32	"... and many forms of cancer, and therefore..."	… and many forms of cancer and other diseases, and therefore… **Outcome**: *It is agreed that many other diseases than mentioned in this section are related to smoking, but for the sake of comprehensiveness only the most relevant ones causing high mortality rates are included.*
L33	Nicotine is certainly responsible (in part) for nicotine/tobacco dependence, but, as of today, there are no data showing its	Nicotine exerts some cardiovascular effects but most of these wane due to substantial development of tolerance. Tobacco toxicity is due to other

	involvement in tobacco related diseases. This widespread misconception is partly responsible for the underuse of nicotine replacement therapies in smokers trying to quit. Using a sentence like "Toxicity is not only related to nicotine itself…" reinforces this misconception.	compounds (e.g. carcinogens) and combustion products like carbon monoxide, and the oxidant gases. **Outcome**: *Partly agreed. In a study by Perkins et al. (JPET 296:849–856, 2001), changes in heart rate and blood pressure after nicotine exposure occurred to similar extent in a group of current smokers, ex-smokers, and never-smokers, indicating that complete tolerance to cardiovascular effects does not occur. The following is included: Tobacco toxicity is mainly due to smoke compounds (carcinogens like polycyclic aromates) and combustion products like carbon monoxide. Nicotine exerts cardiovascular effects like hypertension and increased hart rate*
L33-34	"Nicotine passes the placenta" In fact very few valid data exist on intrauterine nicotine concentrations in humans. They concern essentially amniotic fluid and one study of cord blood concentration. Moreover, NRT is indicated in pregnant women in some countries without any negative signals detected by the post marketing surveillance systems.	Carbon monoxide, not "carbon oxide" Not "polyaromates" but "Polycyclic Aromatic Hydrocarbons (PAHs) and many other toxic and carcinogenic substances in tobacco smoke". **Outcome**: *agreed* **Outcome**: *The phrase is remained, as post-partum PK data obtained from newborns from smoking mothers clearly showed that nicotine passes the placental barrier. (Delia et al, Clin Pharmacol Ther 2000; 67: 458-65).* *A discussion about the risk of using NRT in pregnancy is beyond the scope of this document (see also summary of outcome at the end of the document, section pregnancy).*
L35	The effects of maternal smoking or passive smoking on birth outcomes, and post-natal outcomes should be provided in more detail in order to draw attention to testing new pharmacological treatments also in pregnant women.	**Outcome**: *See also summary of outcome section pregnancy at the end the document, for current vision regarding testing medicines in pregnancy.*
L37		…facial-oral clefts, and sudden infant death syndrome. **Outcome**: *agreed*
L38	The prevalence of smoking "22-47% worldwide" is meaningless and not referenced. European data would be more appropriate for this document. It varies widely between countries (UK, Sweden… vs. Eastern European countries), and as stated (L41-42) with the social-economic status.	**Outcome**: *The source of these data is: Fagerstrom, 2002 (for full reference see references listed in guideline).*
L50	Varenicline is now available in many European countries, and should be added to the list.	…nicotine replacement therapy (NRT), bupropion (Zyban), and varenicline (Champix). **Outcome**: *Agreed. At the time when the draft guideline was out for consultation, registration of varenicline was not yet accepted by the*

		EMEA, and therefore this information was lacking.
L55	Add something on varenicline.	See NICE guidance (UK). **Outcome**: *See comment below (L57-8)*
L57-58	Combination therapy is now generally regarded as best practice. Avoid grading of efficacy as evidence is lacking. Reference to the Cochrane Reviews should be added.	**Outcome**: *This guideline should not be interpreted as treatment guidance, but rather as a guidance for the development of new agents. Therefore all specific details about established treatment options are removed, and information about combined treatment is not included.*
L60	« e.g. NRT in cardiovascular patients… », this sentence suggests that NRT is contraindicated in CV patients. NRT use is actually safe in these patients, and France and UK (other countries are following) have deleted all contraindications for NRT in CV patients.	**Outcome**: *This is a matter of debate. In some EMEA member states, NRT is contraindicated for unstable cardiovascular patients. Specific contraindications are now removed from the text, for reasons mentioned above (L57-8).*
L61	Contraindication for bupropion is not limited to epilepsy, but to all conditions lowering seizures threshold (e.g. alcohol or benzodiazepines withdrawal).	**Outcome**: *Specific contraindications are now removed from the text.*
L66-68	"Moreover…" This sentence should be updated (e.g. including pregnancy contraindication for varenicline and bupropion), and moved to the previous paragraph (L59-61).	**Outcome**: *Specific contraindications are now removed from the text.*
L70	"…alternative pharmacological therapies is encouraged." Current therapies should be promoted more widely; most quit attempts are still made without any support.	…alternative pharmacological therapies and better use of current therapies are encouraged. **Outcome**: *Although supported, this remark is not relevant for this guideline on development of medicinal products, and will not be included.*
L75	"remaining abstinent without drug treatment." Some strongly addicted smokers may not be able to sustain abstinence long term without treatment. The guideline should not close the door to long-term use of smoking cessation therapies (e.g. NRT).	Delete: "without drug treatment" **Outcome**: *This will be changed into: preferably without drug treatment. If patients need to be treated chronically is not an ideal situation, for reasons of safety or adherence.*
L80	"Smoking reduction is not considered an indication target." Smoking reduction "per se" is probably not a good option, but the new indication "reduction to quit" for NRT, licensed in many European countries, has been shown to lead to abstinence and to encourage quitting in previously non-motivated smokers.	The benefit of smoking reduction on health outcome is debatable. However, smoking reduction with pharmacotherapy may be considered as an indication target, if it leads to increase quit attempts and abstinence. **Outcome**: *Smoking reduction as a method to obtain abstinence is an acceptable approach, though it should be demonstrated that in the end indeed abstinence is achieved. The following is added in the Scope section: A more gradual 'cut-down to quit' approach may be applied in the clinical trials in patients not able or willing to quit abruptly, but abstinence is still considered as the ultimate treatment goal and hence the primary outcome should reflect abstinence.*

		See summary of outcome at the end of the document for further justification.
L105-106	DSM-IV-TR or ICD-10 criteria are not used as entry criteria in smoking cessation trials. Only very few used FTND. DSM-IV-TR definition of nicotine dependence in debateable; it shows very poor correlation with e.g. FTND. No evident measure exists to assess nicotine dependence. Usually, the main inclusion criterion in smoking cessation studies is simply the number of cigarettes smoked per day.	**Outcome**: *The shortcomings of diagnostic criteria of DSM-IV and ICD-10 in smoking are acknowledged. The predictive value of relapse of these instruments is reported to be low (Hendricks, Addiction 2008;103:1215-23). The inclusion criterion is now defined as: 'Current smokers with the intention to quit smoking'*
L108	There is probably no example of a clinical study using stratification of the study sample according to naïve/treatment resistant smokers. This can secondarily be analysed in subgroups. Moreover, there is no evident definition of "treatments resistant smoker".	**Outcome**: *It can not be excluded that patients, who had been treated with other pharmacological treatments but failed, might be more treatment resistant to the new drug than naïve subjects. Randomisation, and stratification based on this factor, could prevent bias.* *New text: The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. In principle, inclusion should be as broad as possible. Subjects may be stratified according to their level of nicotine dependence, or the earlier use of other pharmacological treatments.*
L122-123	What is the justification to include a "general health score" for efficacy studies? Phase II and III efficacy studies are realised in smokers without psychiatric or other comorbidities. This allows keeping the number/arm at a realistic level. Inclusion of comorbidities would increase the number needed to show a difference leading to huge numbers by arm. Studies in smokers with comorbidities are realised in the second wave of clinical trials.	**Outcome**: *As stated in the guideline, it is not considered necessary to perform efficacy trials in special populations with co-morbidities. The safety profile of a new product should however be known for cardiovascular and pulmonary compromised smokers, as these patients form a potential users group. Safety trials in (former) psychiatric patients may need to be performed if specific safety concerns are expected, depending on the pharmacology of the drug.* *Depending on the strategy of the Company, inclusion of cardiovascular and pulmonary comprised patients may be considered earlier in development, e.g in confirmatory trials, or later. Documentation of the health status at baseline is then useful.* *Documentation of the baseline health status is also needed to verify whether subjects are included according to the inclusion criteria from the protocol. Baseline data may be useful to evaluate safety outcomes from the study.*
L126-129	SRNT guidelines, or Russell's standard defined the different types of abstinence for clinical studies. What is meant here by "total abstinence"? Hughes et al. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob Res, 2003; 5 : 13–25.	**Outcome**: *The primary endpoint is defined as: continuous abstinence rate without slips or episodes of relapse to smoking throughout the follow-up period.*

	West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005 Mar;100(3):299-303.	
L130-133	"Therefore the primary endpoint should be the persistent abstinence rate off drug until 1 year after the end of the initial treatment period." There is a debate about the necessary length of follow-up to judge on efficacy of a smoking cessation treatment. A 1 year follow-up is usually accepted as a secondary endpoint and not a primary one. For this and other aspects of measuring abstinence in clinical trials, see SRNT recommendations or Russell's standard (references above)**.** In any case, a follow-up of 1 year **after the end** of the initial treatment period has never been used (the classical option is **after the beginning** of the treatment period). Moreover, if one is considering a 6 month or 1 year pharmacological treatment this would considerably increase the cost of clinical trials and deter any development of new therapies. With available treatments, it is usually accepted that relapse is relatively parallel in both active and placebo treatment groups if the randomisation has correctly been done. Long-term abstinence rates may then be possibly extrapolated from a shorter follow-up after the end of treatment (survival curves). Moreover, there is strictly no pharmacological example for a drug leading to long-term efficacy if the efficacy is not related to structural changes (like chemotherapeutics, irreversible enzyme inhibitors, etc). In order to accelerate the development of new therapies, we suggest that the main outcome measure be the end of treatment abstinence rate with specific follow-ups to look at withdrawal effects of the treatment or at late occurring adverse events. In fact, off-treatment periods are not under control and several confounders may affect outcome. Moreover, because of the increased likelihood of drop outs during follow-ups, the power to show a difference at follow-up is decreasing thus necessitating randomising a large number of participants. **This leads to exposure of a high number of participants to an investigational drug/treatment. This raises ethical issues.**	Outcome**:** *The requirement of 1 year abstinence from end-of-treatment has been adapted. Now the active treatment period may be taken into account in the assessment of efficacy.* *Starting point of evaluating efficacy may be Target Quit Data and/or end of the 'grace period', a period in the initial phase of active treatment where slips are allowed. For long-term treatment options exceeding 6 months of active treatment, the off-drug follow-up period should be minimal 6 months, as relapse rates tend to increase after end of treatment.* *A period of one year was also chosen, as only sustained abstinence over a long period is considered clinical relevant and relapse rate tend to stabilize after 1 year.* **Outcome**: *Extrapolation of relapse rate beyond the observation period is not acceptable for trials on new drugs (where this guidance intended for), as it is an unknown and unprecedented factor. Treatment free relapse rates at long-term cannot be reliable predicted from the active-treatment phase.* *If chronic therapy is indicated, this should be demonstrated by randomised treatment-withdrawal studies.* **Outcome**: *If randomization is well applied, it is not expected that co-founders would influence the placebo or active treatment arm differently in the off-treatment follow-up period, and that this would lead to bias.* *Based on earlier studies, it is expected that data of 1 year follow-up after randomization (including 6 months off-drug) is feasible and clinical meaningful endpoint. Studies with established treatment options (NRT, bupropion, and varenicline have shown that 1 year efficacy trials are feasible, even though the active treatment period was relatively short in these trials.* *For further justification, see summary of outcome at the end of the document for comments.*
L134		carbon monoxide, not "carbon oxide"

		Outcome: *text has been changed accordingly*
L136	"- Abstinence rate at the end-of-treatment period" This should be considered as a primary endpoint, not secondary.	Move under 4.2.1 **Outcome**: *See response to comments on L130-133 above*
L142	"vivid dreams" is not a nicotine withdrawal symptom (see DSM-IV-TR)	Delete: vivid dreams **Outcome**: *Agreed. Vivid dreams should be reported as psychiatric side effect rather than withdrawal symptom. Text has been changed accordingly.*
L144-145	Please cite correctly the name of withdrawal scales.	Give references for the scales mentioned. **Outcome**: *Text is revised accordingly. A reference to the literature is supplied*
L148	"…long-term data [craving] (e.g. 1 year after treatment) are needed. For a specific claim regarding craving, such a long-term follow-up would be most inappropriate. Even if craving can manifest years after smoking cessation, no treatment (except chronic treatment) could show efficacy on long-term craving if it is not administered (see above).	For a specific claim regarding craving, only short-term data (e.g. end of treatment) are needed. **Outcome**: *Text regarding long-term craving data will be deleted, as this is not applied in trials thus far. The following text is included: 'Measuring withdrawal symptoms and craving is not only of interest during active treatment, but also in the period immediately after the subjects become off-drug.'*
L155	"Craving studies may establish the proof of concept." This is contradictory with the previous item, as a proof of concept study is usually a short-term study.	**Outcome**: *See comments to L148 above*
L180-184	"Usually a TQD is set within two weeks after initiating treatment". No general rule applies. This pre-TQD treatment period was introduced with non-NRT medications in order to match TQD with steady state plasma levels of the drug or steady-state of the pharmacological effect. For NRT e.g. this is not true (see labellings). Here, there is a mix up between a pharmacological consideration (reaching steady-state) and the grace period which is a clinical issue and independent of obtaining steady state.	**Outcome**: *Agreed. The following is added: though a more prolonged period may be chosen depending on pharmacological properties of the product.*
L192	"1 year off drug, » see comments for L130-133.	**Outcome**: *See comments above (130-3)*
L199	Same as above.	**Outcome**: *See comments above (130-3)*
L203-204	"For evaluation of an additional benefit of maintenance treatment, the follow-up of 1 year off drug is, again, obligatory." Again, this would considerably increase the cost of clinical trials and deter any development of long-term therapies.	**Outcome**: *For treatment exceeding 6 months of therapy, the follow-up should be at least 6 months off-drug.*

L216-217	"Studies in children are not deemed necessary, since smoking is not a major public health problem of this age group." This is probably true in Europe, but may not be elsewhere.	**Outcome**: *This guideline is intended for products on the European market, so this remark is indeed relevant.*
L220-225	There are no data to support the statement that the pathophysiology of nicotine dependence is not different from that of adults. Tobacco dependence develops during adolescence. Thus, it is highly important to address the smoking problem as early as possible using both non-pharmacological but also pharmacological methods. In order to include adolescents in the labelling, not only pharmacokinetic and but also efficacy data may be necessary along with safety data.	**Outcome**: *Agreed, text is changed into: Cravings and withdrawal symptoms may occur rapidly after the first experience with nicotine even before daily use. In general, adolescents may be less motivated to stop smoking, which may affect efficacy outcomes. Studies in adolescents may be considered, but preferably once broad post-marketing experience in adults has been obtained. The generation of pharmacokinetic and safety data is relevant if adolescents are included in the labelling. Depending on the pharmacology of the drug, specific safety measures regarding growth and/or sexual maturation, and mood disorders, may be considered to be monitored in adolescents.*
L234	We agree that specific efficacy studies in psychiatric patients should not be mandatory but such studies should be encouraged. This would change the current situation: very few therapeutic trials have been run in these populations leading to totally insufficient data.	**Outcome**: *This point of view is reflected in the guideline.*

COMMENTS FROM Royal College of Physicians

GENERAL COMMENTS

The Royal College of Physicians is concerned that the Guideline as currently drafted may serve as a barrier to the development of more effective medications for smoking cessation, rather than facilitate good practice.

The guideline appears to have been drafted without adequate reference to existing practice, as represented by, for example, the Cochrane Collaboration, the recommendations of the Society for Research on Nicotine and Tobacco (SRNT), or established criteria of the US Food and Drug Administration. The implicit model of treatment adopted is one akin to the use of antibiotics to combat infection, where a strictly limited period of treatment may result in cure. The relevance of this for a chronic relapsing condition such as nicotine dependence is open to serious question. The membership of the Efficacy Working Party of the CHMP does not appear to have included sufficient expertise in the area of smoking cessation. The result is that, in our view, the draft guideline is deeply flawed throughout, and unfit to serve its purpose. In the circumstances, the best way forward may be to postpone issuing the guideline, while bringing in suitable expertise to develop revised proposals.

See summary of outcome at the end of the document for statements why smoking reduction is not considered a suitable endpoint for new products.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
L33	L33: "Toxicity is not only related to nicotine itself….".	This wording actively promotes the widespread popular misapprehension that the adverse health effects of cigarettes are largely attributable to nicotine. Suggest 'However, the contribution of nicotine to the toxicity of smoking is probably negligible; it is the hundreds of other carcinogens and toxins in smoke that causes the harm' **Outcome**: *The text is changed into: Tobacco toxicity is mainly due to smoke compounds (carcinogens like polycyclic aromates) and combustion products like carbon monoxide.*
L34		Carbon monoxide, not "carbon oxide". **Outcome**: *The text is adapted accordingly*
L38	L38: "The prevalence of smoking in adults is currently estimated to be between 22-47% worldwide".	These % are unhelpful, as it is unclear to which populations they refer or the source of the data. Higher prevalence is seen in some populations (in men in China, for example), and lower in others (e.g. Canada, Sweden and Australia). **Outcome**: *The source of these data is: Fagerstrom , 2002 (for full reference see references listed in guideline). Detailed data about epidemiology of smoking are not considered of major importance for this guidance document on development of new products for treatment of smoking.*
L60	The text here suggests indicates that cardiovascular disease is a contraindication for NRT. In fact, the available data suggest that NRT is safe in patients with CVD, and regulators are increasingly relaxing earlier more cautious approaches to NRT use in heart patients (for example the UK and France).	There is no particular contraindication for NRT in stable cardiovascular disease. **Outcome**: *This is a matter of debate. In some member states, NRT is contraindicated for unstable cardiovascular patients. Specific contraindications are now removed from the text.*
L74-5	Abstinence without drug therapy Achieving abstinence from smoking should be the primary objective, and abstinence from all nicotine products a secondary objective. It is true that cutting down on cigarette consumption by itself is of doubtful value to health, but there is evidence that cutting down using NRT is less likely to lead to compensation and can encourage quitting and NRT for this use is licensed in	**Outcome**: *This will be changed into: preferably with drug treatment. If patients need to be treated chronically is not an ideal situation, for reasons of safety or adherence.*

	numerous countries in the EU (UK, France, Sweden, Denmark, Italy, Austria, Belgium). Complete substitution of smoking by medicinal nicotine, even if resulting in long-term medicinal nicotine use, offers substantial health benefits.	
L130-3	One-year abstinence as primary endpoint. No good case is made for opting for "persistent abstinence off drug until 1 year after the end of the initial treatment period" as the primary endpoint. We would agree that longer duration outcomes are more likely to reflect the true efficacy of a treatment in practice, and suspect that that may be the rationale behind this recommendation. However, adoption of this primary endpoint would increase the cost of trials substantially, not only because of the additional time involved but also because much larger sample sizes are necessary to detect differences in the lower abstinence rates that apply at one year in comparison with, for example, three or even six months. The proposal therefore imposes needless delays and financial obstacles to the licensing of potentially valuable treatments. It would also in practice prevent the assessment of interventions in minority and hard-to-reach groups among whom trial participation can be very difficult to sustain. No regulator currently uses this as the primary endpoint. Available data from existing trials indicate that, although relapse to smoking occurs throughout the first year after smoking cessation, the basic picture as regards relative treatment efficacy is established early on, and does not change appreciably in relative terms (other than through loss of statistical power through patient drop out) with continued follow-up. This provides ample justification for current regulatory approaches, which take abstinence at 3 months or so from treatment inception as the primary endpoint, with abstinence up to 1 year as a secondary outcome.	Outcome**:** *The requirement of 1 year abstinence from end-of-treatment has been adapted. Now the active treatment period can be taken into account in the assessment of efficacy. Starting point of evaluating efficacy may be Target Quit Data and/or end of the 'grace period', a period in the initial phase of active treatment where slips are allowed. For long-term treatment options exceeding 6 months of active treatment, the off-drug follow-up period may be as short as 6 months.* *A period of one year was also chosen, as only sustained abstinence over a long period is considered clinical relevant and relapse rate tend to stabilize after 1 year.* *Studies with the major established treatment options (NRT, bupropion and varenicline) have shown that 1 year efficacy trials are feasible, even though the active treatment period was relatively short in these trials.* *The main scope of this guidance is new agents that are developed for treatment of smoking. For new agents, long-term efficacy, which is considered relevant, cannot be predicted from short-term follow-up data, and therefore a long-follow up period is required.* **Outcome**: *Regarding comments on prior decisions by regulators and consistency in decision making: for the most recent product, varenicline, the 1 year abstinence data were considered as co-primary outcome by the CHMP. One year data were also available for the bupropion dossier.* *For further justification, see summary of outcome at the end of the document.*
L148-9	Data on craving. It is quite inappropriate to require data on craving 1 year after treatment for a specific claim regarding craving to be made.	**Outcome**: *This requirement has been dropped*
L180-4	"…acute withdrawal and craving has subdued " Presumably subsided is meant. But why withdrawal and craving should reduce in the 'grace period' when "no complete abstinence is expected" is not clear.	**Outcome**: *The US term 'subdued' will be replaced by 'subsided'* **Outcome**: *Acute symptoms of withdrawal and craving are expected to decline once the patient persist abstinence or reduce smoking level, and once the patient is stabilized on treatment. Text is remained*
L203-4	"for an evaluation of an additional benefit of maintenance treatment, the follow-up of 1 year off drug, is, again, mandatory".	**Outcome**: *Off-drug follow-up data are required, as relapse rates tend to increase after ending active treatment. It has been adapted into 6 months off-drug. See summary of outcome at the end of the document*

	For a trial of drug treatment for 12 months, this would require assessment of the primary abstinence outcome 2 years after treatment initiation. This requirement could have the effect of deterring developing and testing of treatments, through excessive cost and delay.	*for further justification.*

COMMENTS FROM SMOKING PREVENTION GROUP OF THE SPANISH RESPIRATORY SOCIETY (SEPAR)

GENERAL COMMENTS

We would like to congratulate the working group of this guideline and want to express our thanks for letting us to give some comments to this draft.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
LINE No 60	No type of NRT is contraindicated in smokers with stable cardiovascular disease. It was not possible to demonstrate any increase in cardiovascular diseases in studies conducted over 5 years in healthy individuals who have used nicotine gum (Murray PR., Bailey W et al. Safety of nicotine policrilex gum used by 3094 participants in the lung health study. Chest 1996; 109: 438-445.). In addition, no evidence of high risk of alterations in the ECG, arrhythmias, angina or sudden death has been found in cardiovascular patients who have used NRT during their smoking cessation process (Joseph A., Norman S.. et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N. Engl J Med 1996; 335: 1792-1798.). It has also been indicated that NRT has less risk of producing acute myocardial infarction than smoking cigarettes (Joseph A., Norman S. et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N. Engl J Med 1996; 335: 1792-1798.)	NRT in cardiovascular patients should be deleted **Outcome**: *This is a matter of debate. In some member states of the EMEA, NRT is contraindicated for unstable cardiovascular patients. Specific contraindications are now removed from the text, as this document is not meant as a treatment-guidance.*
Line No 80	Recent studies have shown that a certain number of smokers want to quit smoking. However, with the present approach to smoking cessation treatment, that is abrupt and definitive cessation of tobacco consumption, only a few try it. On the contrary, a greater number of smokers are more willing to significantly reduce the	Smoking reduction as a previous step to quit should be considered as an indication target. **Outcome**: *Smoking reduction is indeed not an acceptable treatment aim or outcome for a clinical trial on new products. In the Scope section it is*

	number of cigarettes smoked daily and than to stop smoking abruptly and definitively (Etter JF, Perneger T, Ronchi A. Distributions of smokers by stage: international comparison and association with smoking prevalence. Prev Med 1997; 26: 580-585 and CDC. Cigarette smoking among adults – United States, 2000. MMWR 2002; 51: 642-645 and Hughes JR et al. Interest in gradual reduction. NT&R 2007; 671-675) Smoking reduction as a previous step to quit should be considered. On the other hand, the benefit of smoking reduction on health outcome is not clear.	*stated that a cut-down-to-quit approach may be applied, but the treatment goal remains abstinence.*
Line No 132	Definition of primary outcome should be reconsidered. Normally, the efficacy of a medication to cure or alleviate a chronic disorder is measured during the time the medication is taken. The efficacy of a medication to control hypertension is measured after several weeks or days of taken this medication. The efficacy of this medication is never measured after several months of having stopped it. Tobacco dependence is a chronic disorder. The efficacy of medications that can help smokers to combat tobacco dependence should be measured while these medications are taken. It should be considered to prolong the time taking medication. (Harris T, Fiore MC. Pharmacotherapy for treating tobacco dependence. CNS Drugs 2002; 16: 653-662). Some studies have found that prolonging the use of NRT could increase the efficacy of these products. (Murray RP et al. Prevent Med 2000; 30:392-400) Other studies using varenicline have had similar results.(Tonstad S et al. Effect of manintenance therapy with varenicline on smoking cessation. A randomized controlled trial. JAMA 2006; 296:64-71) We have to take into account that if we are looking for increasing the efficacy we should deviate from the protocol of clinical trials that were designed primarily to determine whether the medications were of sufficient benefit to merit approval by regulatory agencies, not necessarely to optimize efficacy. (Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med 1995; 333:1196-203)	"The primary endpoint should be the persistent abstinence rate off smoking while subjects are taking medication. Abstinence rates until 6 and 12 months after ending medication should also be considered but not as primary endpoints" **Outcome**: *The requirement of 1 year abstinence from end-of-treatment has been adapted. Now the active treatment period can be taken into account in the assessment of efficacy. Starting point of evaluating efficacy may be Target Quit Data and/or end of the 'grace period', a period in the initial phase of active treatment where slips are allowed.* *The off-drug period should be taken into account as well, as relapse tend to increase after drug withdrawal, and only sustained abstinence over a considerable period is considered clinical relevant. For long-term treatment options exceeding 6 months of active treatment, the off-drug follow-up period may be 6 months.* **Outcome**: *The scope of the guidance is not specifically short-term treatment options, but also long-term treatments. If a chronic treatment is considered useful, this should be evaluated by randomised parallel withdrawal studies, where treatment continuation after the regular prescription period is compared to placebo (see section 4.3.3 c of the revised guidance).*
From line No 145 to line No 149	The pattern of smoking withdrawal is different for each individual. Piasecki et al found that smokers who experience a gradual elimination of withdrawal symptoms are less likely to relapse than those who experience a withdrawal symptoms that increase with time or remain elevated over a period of time. (Piasecki et al. J Abnorm Psychol 2000; 100:74-86.). Taking into	"For a specific claim regarding smoking withdrawal , both short-term and long-term data are needed, dependent on the time medication is taken" **Outcome**: *The whole section regarding craving is deleted. See also answers to comments made by SNRT Europe, line 145-9*

	account this heterogeneity of withdrawal patterns over time, it is necessary that therapy to treat withdrawal must likewise be heterogeneous and individualised not relying on the "one size fits all" principle. (Harris T, Fiore MC. Pharmacotherapy for treating tobacco dependence. CNS Drugs 2002; 16: 653-662). So, to measure the efficacy of a determine medication to control smoking withdrawal, we should use short-term data. We should measure the efficacy of a determine medication while the subject is taking this medication. It is not appropriate to measure the efficacy of a determine medication to control smoking withdrawal several month after having stopped this medication. The time of measuring the efficacy of a determine medication to control smoking withdrawal should be limited to the time while this medication is taken.	
From line No 173 to line No 177.	Regarding the use of a comparator-controlled parallel group, you should take into consideration that NRT has proved its efficacy and safety in many RCT-s during the past 25 years. (Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical Practice guideline. Rockville, MD:US Department of Health and Human Services. Public Health Service. June 2000.).	**Outcome**: *The choice of the comparator (NRT, bupropion, varenicline) is up to the Company. In principle, these three comparators are all effective and established, but have a different safety profile. The choice of the comparator may preclude certain patients' groups for which the drug is contraindicated.*
Line No 203.	Testing the efficacy of prolonging pharmacological treatments is an issue that should be analysed in next RCT-s. Taking into account the considerations that we have made in line No 132, we proposed to change the wording as indicated.	"For the evaluation of an additional benefit of maintenance treatment, the primary endpoint should be the persistent abstinence rate off smoking while subjects are taking medication. Abstinence rates until 6 and 12 months after ending medication should also be considered but not as primary endpoints" **Outcome**: *The required follow-up period off-drug is shortened to 6 months. See also summary of outcome at the end of the document for comments.*
Line 234	.Psychiatric patients are special smokers. Most of them smoked many cigarettes per days, most of them are more dependent on nicotine than "healthy smokers". Psychiatric patients experience different patterns of withdrawal syndrome that can make them difficult to quit. (Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical Practice guideline. Rockville, MD:US Department of Health and Human Services. Public Health Service. June 2000. and Hughes JR. Depression during tobacco abstinence. NT&R. 2007; 4:443-446).	"Specific efficacy studies in psychiatric patients are needed" **Outcome**: *It is expected that mechanism of action in the target population is similar in special patient groups. Response rates may be different by co-morbidity but if a treatment is truly active, a difference in response rate between active and placebo is expected as well, although at a different level. Therefore separate efficacy studies are not deemed necessary in patients with psychiatric co-morbidity. If a product is effective in the general smokers population these patients should not be denied treatment or even contraindicated, unless there are specific safety reasons why a product cannot be used in psychiatric patients. Therefore, specific safety studies in (former) psychiatric patients are required, when*

		it is expected that agent may worsen psychiatric symptoms (e.g mood disorders, agitation, pharmacokinetic interactions with psychiatric drugs). *The same argumentation applies to COPD patients. See below.*
Paragraph 4.4.	We think that it is necessary to include a paragraph referring the special characteristics of COPD smokers or smokers with pulmonary disorders. The rationale to include this paragraph is as follows: i) Two population-based studies have found that COPD smokers had a higher grade of nicotine dependence than average smokers.(Jiménez Ruiz CA et al. Smoking. Characteristics. Differences in attitudes and dependence between healthy smokers and smokers with COPD. CHEST 2001. 119: 1365-1370 and Shahab L et al. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61:1043-7.) The first study analysed a representative Spanish population, and it was found that smokers with COPD had a higher dependence on nicotine than healthy smokers, their FTND-score was 4.77 vs 3.1, respectively (p< 0.001). Similar results were found by the second study that was carried out in UK. A population-based study analysed a representative sample of 8215 subject aged more than 35 years old. They found that smokers with COPD had higher degree of nicotine dependence than healthy smokers. (Shahab L et al. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61:1043-7.). ii) Moreover, it has been analysed the data to show the value of the degree of nicotine dependence, measured by FTND score, as a predictor of the development of COPD in smokers. It was found that each additional point in the FTND score was significantly associated with an increase of 11% in the probability of developing COPD (Jiménez-Ruiz CA, et al. Can cumulative tobacco consumption, FTND score, and carbon monoxide concentrations in expired air be predictors of chronic obstructive pulmonary disease? Nic & Tob Res 2004; 6: 649-53.) iii) Anxiety, depressed mood and even depression have been associated with COPD. Wagena et al carried out a prospective population based cohort study. They found that 10% of the non-smoking COPD/Asthma patients were depressed while 29% of the smokers rated themselves as depressed. In the COPD/Asthma group depressed mood was twice as common as in the control	"*Smokers with COPD and other respiratory disorders"* " Smoking is the single most relevant risk factor for COPD and for other respiratory disorders. Smoking cessation is the most effective treatment for preventing or decreasing the progression of COPD. Furthermore, smoking cessation programs may lead to a significant reduction of mortality in people affected by COPD and other respiratory disorders. Many studies have shown that smokers with COPD have special characteristics that can make them more difficult to quit and may require more assistance to be successful. Specific efficacy and safety studies in respiratory patients are needed. Potential pkarmacokinetic interactions with habitual medication of these patients should evaluated" **Outcome**: *The safety profile of the new agent should be evaluated in pulmonary compromised patients, as these patients form a potential users group. This requirement will be further emphasized in the text under a separate subheading in section 4.5.1. In section 4.3.1, it is included that potential PK interactions with medications typically used in this patients' group should be evaluated.* *Specific efficacy studies in COPD patients are not required.* *In principle all COPD patients willing to quit (or cut-down-to-quit) should be offered pharmaceautical treatment options, disregarding whether efficacy is lower than the general population, and provided that the new product can be safely used in this special population. See also decision for psychiatric patients, Outcome Line 234 above.*

	group of smokers with other chronic disorders and 4 times as common as in healthy smokers (Wagena EJ, et al. Psychological distress and depressed mood in employees with asthma, chronic bronchitis or emphysema. A population-based observational study on prevalence and the relationship with smoking cigarettes. Eur J Epidemiol 2004 ; 19 : 147-153.) iiii)The European Respiratory Society considers that looking for new therapeutic strategies to help smokers with respiratory disorders to quit should be a main objective. (P Tønnesen, et al. Task Force Recommendations: Smoking cessation in patients with respiratory diseases: A high priority, integral component of therapy. Eur Respir J. 2007). Taking into account these comments it should be considered that smokers with COPD may require more assistance to quit. We proposed to include a paragraph as we indicated.	

COMMENTS FROM National Association of Women Pharmacists (UK)

GENERAL COMMENTS

Our comments are exclusively of a general nature. We note that there is a requirement for the gender of trial participants to be recorded and reported. However, we consider that the importance of gender issues needs to be stressed further. The weight of published evidence showing differences between the genders with regard to development, maintenance and cessation of smoking is sufficiently great to justify this. We doubt if it is appropriate to make a detailed case to support our view, but we consider that it is supported by two recent papers. A paper from the US National Institute on Drug Abuse (Wetherington CL, Exp. Clin Phamacol 2007 15(5) 411-417) reported a shift in US thinking away from merely considering pregnancy-related issues, so far as women and substance dependence are concerned. The paper concluded that in the field of drug abuse as a whole "the burden of proof is shifting from having to defend why sex-gender differences should be studied to having to defend why they should not". A paper reviewing cost effectiveness of nicotine therapies across a spectrum of European and non-European countries (Cornuz J et al Tobacco Control 2006 15(3) 152-159) reported big differences between genders, based on commonly used indices. Information of this type is used by those funding healthcare, but good clinical data is required for proper interpretation and evaluation of cost efficacy data.

Outcome: *Regarding inclusion criteria: Both males and females should be included. The guideline (section 4.1, selection of subjects) is adapted accordingly.*

Outcome: *It is not supported that new agents will be tested in pregnant women, before broad post-marketing experience has been obtained. Several side-effects become only obvious once a large population has been exposed. In this guideline on smoking, reference is made to the Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data EMEA/CHMP/313666/2005). According to the latter guideline, women and children who are (accidentally) exposed during pregnancy should be monitored, as well during pregnancy as thereafter. Companies are encouraged to perform epidemiological studies on pregnancy post-marketing, but companies cannot be forced to expose pregnant women to new medicinal products.*

COMMENTS FROM EFPIA

GENERAL COMMENTS

Objections to proposed primary endpoint:
Although long term or permanent smoking abstinence is a universal goal in the treatment of smoking addiction, this is generally achieved in two stages. The first is the act of quitting itself and overcoming the accompanying discomforts such as nicotine withdrawal symptoms. Most pharmacotherapies are acute treatments that address this phase of smoking cessation and are generally labelled with the indication "for smoking cessation treatment". This is followed by a much longer phase that can be considered maintenance of abstinence / absence of relapse. Nicotine addiction is known to be a chronic relapsing condition that frequently requires repeated attempts before long-term abstinence is achieved. The draft guidelines propose that the primary efficacy endpoint of a clinical smoking cessation trial should be biochemically verified complete abstinence for one year after end of treatment. This is demanding that the primary proof of efficacy for a short-term intervention for a chronically relapsing condition should be long-term success!

That the efficacy of a drug should be assessed on events that occur over a period of many months during which there is no exposure to the drug poses an unrealistically high hurdle. Potentially a treatment that has a significant and substantial treatment effect during treatment could be considered to have no merit. A review of clinical trials in the Cochrane review of nicotine replacement therapy for smoking cessation (2) shows that, individually, the majority of trials would not have achieved even the somewhat lesser mark of continuous abstinence at one year from study start, and yet nicotine replacement therapy is widely accepted as a first line treatment for smoking cessation (2, 3, 4).

There are no scientific data relating long-term outcome differentially to the initial treatment. The rate of relapse to smoking is similar irrespective of the method by which cessation was achieved, and so short-term results are highly predictive of long-term post-treatment abstinence rates. Consequently, a substantial period of abstinence at the end of treatment is the most suitable and appropriate measure for the primary clinical trial endpoint for smoking cessation treatment. While the duration of abstinence of abstinence that constitutes a successful 'quit' may be debated (and periods as short as a few days have been used in the literature I WILL FIND REFERENCE), a period of 4 weeks of complete abstinence at the end of the treatment period has become an acceptable standard and we propose that it should remain so. The duration of treatment would depend on the pharmacokinetics and pharmacodynamics of the pharmacotherapy, but to be considered "acute treatment" a maximum treatment duration of 12 weeks would be reasonable.

The durability of smoking cessation is nonetheless of considerable interest and relevance, and therefore continuous abstinence rates of 6 months and 12 months duration should be included in all clinical trials as important secondary endpoints. Recently, a group of experts with extensive experience in smoking cessation treatment have proposed follow-up for 6 months and 12 months from the target quit date or from the end of the grace period as a common standard (Russell Standard) for clinical trial outcome criteria (4). It is generally acknowledged that the benefits of smoking cessation begin to accrue from the beginning of abstinence and that even brief periods of success can increase the confidence of quitting in subsequent attempts. Long-term abstinence assessed with "time-to event" or Kaplan-Meyer survival analyses should be considered acceptable alternatives, especially considering these are based on the more efficient and optimal use of all observed data.

Most long term follow-up to date has considered even the smallest lapse as a return to smoking. It would be helpful if the guidance provided practical and realistic definition of relapse that would be more indicative of a return to regular smoking. This would be particularly important for medications that act by preventing a lapse from becoming a relapse. If the lapse itself already classifies the subject as a failure, there is no opportunity to demonstrate the efficacy of the intervention.

The additional challenges associated with a 1-year follow-up period as a primary analysis that include patient recruitment/retention and sample sizing are also a barrier to the development of smoking cessation pharmacotherapies. The requirement for a long-term follow-up period has a direct impact on patient

recruitment (patients are less likely to consent to a trial knowing they are required to visit the clinic long after treatment has stopped). And success or failure of long-term observation becomes essentially a function of patient retention. Patient retention is more difficult when no treatment is involved. This is especially true for patients who do not respond to the initial treatment course.

References:
(1) West R, Hajek P, Stead L, Stapleton J. (2005) Outcome Criteria in smoking cessation trials: proposal for a common standard. Addiction 100:299-303
(2) Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004;3: Art No: CD000146.DOI: 10.1002/14651858. CD000146. Pub 2.
(3) Fiore MC, Bailey WC, Cohen SJ et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville, MD: US Department of Health and Human Services. June 2000.
(4) NICE: TA39 Smoking cessation – bupropion and nicotine replacement therapy: Guidance. Issue Date: March 2002 Review Date: March 2005. [http://www.nice.org.uk/30590].

Outcome:

Only abstinence that can be maintained for a prolonged period is considered clinical relevant. Confirmation is needed that not only short-term abstinence is achieved, and patients returned to smoking again to the same extent as placebo after 1 year. For establishing efficacy, the off-drug period is considered relevant, as relapse rates tends to increase immediately after ending active treatment, and long-term relapse can not be predicted from short term results, at least for new treatment options. A period of one year is chosen as relapse rate tend to stabilize after one year.

Time to event analysis in smoking is not considered the best approach. Difference in survival curves, i.e. postponing relapse is meaningful knowing that relapse rates at 1-2 year are high. Hence analyses of responder rates (i.e. a responder is a subject who remained abstinent till 1 year of follow-up) provide a more meaningful endpoint.

The endpoint has been adapted in a way that the 1 year period refers to 1 year after randomization instead of 1 year follow-up off drug. Abstinence under active treatment is also relevant, and may be taken into account in efficacy measurements. The start point for measuring abstinence will be the Target Quit Data or the end of a predefined grace period, where slips are allowed, till one year after randomization. For long-term treatment options exceeding 6 months, an off-drug follow-up period of 6 months should be taken into account instead of 12 months as required in the draft version of the guideline. It is expected that feasibility of trials will be improved by these adaptations.

The conclusion that the endpoint would not be feasible, and an unrealistic hurdle is not agreed. Several studies with varenicline, NRT, and buprion showed that they were superior over placebo after 1 year, even though the studies were not powered for 1 year outcome, and active treatment period was short.

As relapse rates are high in smokers despite therapy, a product can be developed to prevent relapses, but another study design (with placebo-controlled treatment withdrawal) is then needed to demonstrate that maintenance of effect is indeed achieved. This is described in section 4.3.3c.
Studies on re-treatment in relapsed smokers are encouraged in the guideline.

The scope of the proposed guidance is limited. It assumes the current drug treatment paradigm of short-term treatment, followed by a long-term observation period without allowing for other treatment paradigms, including continuous or long-term drug treatment or pulse or intermittent (weekly, monthly, or yearly) therapy. Furthermore 'Reduce to quit' treatment is an accepted indication for some forms of NRT and supported by clinical practice, particularly in recalcitrant smokers. As noted in the Cochrane Review of NRT for smoking cessation (5), "The use of two forms of NRT, gum and inhaler, has now been approved by licensing authorities in some European countries for this cessation approach, described variously as 'Reduce to Stop' or 'Cut Down to Quit'. Smoking reduction has been shown to increase the likelihood of a future quit (6).

Outcome:
The cut-down-to-quit approach is included in the scope section of the guideline:
"Smoking reduction is not considered an indication target. The benefit of smoking reduction on health outcome is debatable. A more gradual 'cut-down to quit' approach may be applied in the clinical trials in patients not able or willing to quit abruptly, but abstinence is still considered as the ultimate treatment goal and hence the primary outcome should reflect abstinence."

For line extensions of existing actives, bioavailability/bioequivalence studies (CPMP/EWP/QWP/1401/98) should be considered to suffice in lieu of formal safety and efficacy studies.
Outcome: *The following is added: 'For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed'.*

References:
(5) Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub3.
(6) John R. Hughes, Matthew J. Carpenter. 2006. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. Nicotine & Tobacco Research Volume 8 (6) 739–749.

SPECIFIC COMMENTS

1. INTRODUCTION (EXECUTIVE SUMMARY)

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Section 1.2 Estab. treatment	It is not appropriate for a guideline on development of new products to provide commentary on the relative effectiveness or limitations of existing products. It is unlikely the guidelines will be updated as new treatments for smoking cessation are developed. The encouragement for development of additional pharmacological therapies should be included in the introduction.	Delete section or edit as follows: The efficacy of ~~both~~ NRT, ~~and~~ buproprion ***and varenicline has been established***. ~~is rather similar, and in~~ Many trials ~~it is~~ ***have*** proven that these products are superior to placebo. **Outcome**: *Any specific recommendation regarding the use of established treatment options have been deleted.*
Lines 48-55	The description of established treatments in this paragraph discusses NRT and bupropion exclusively. First line treatments currently available include varenicline.	Add varenicline as available option and provide information similar to NRT and bupropion **Outcome**: *Varenicline is added. Regarding the use of established treatment options have been deleted.*
Lines 53-54	Bupropion is not a serotonin re-uptake inhibitor nor is it a non-competitive nicotine receptor antagonist.	Delete this statement **Outcome**: *The text has been adapted accordingly* Moreover there are limited treatment options for some patient groups such as ~~cardiovascular~~

Line 60 Lines 66-67	NRT is not contraindicated in cardiovascular patients in some European markets therefore this example may cause confusion. The recent positive recommendations of the UK Committee on Safety of Medicines' Working Group on NRT http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2022933&ssTargetNodeId=221) on labelling for use in cardiovascular patients is being increasingly accepted by other member states during MR/DC procedures. Hence treatment options in this group of smokers are no longer so limited.	~~patients and~~ patients once diagnosed with psychoses or epilepsy **Outcome**: *Specific product information regarding contraindications is deleted, as this document is not intended as a treatment guidance.* *(Of note, some member states have contraindications for unstable cardiovascular patients, but it is not considered relevant to discuss this in detail in this guidance document).*
2. SCOPE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Section 2 Scope Lines 72-85	The scope of the document does not reflect the state of the science in the area of nicotine dependence. While it is true that drugs currently on the market focus primarily on acute treatment for abrupt cessation and relapse prevention, the ultimate goal of lifetime abstinence could also be achieved with other treatment modalities such as pulsed treatment, long-term treatment as well as 'Reduce to Stop' treatment. **SEE GENERAL COMMENTS**	**Outcome**: *The reduce-to-quit approach is included. However, the ultimate treatment goal and hence the primary outcome is still considered abstinence.*
4. MAIN GUIDELINE TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Section 4.1 Subject selection Lines 107 -110	Formal stratification adds complexity to trial design and increases costs and timing and as such could hinder the stated desire to encourage the development of alternative pharmacological therapies (Section 1.2 Ln 70) Moreover, requiring stratification by "naïve" and "resistant" is unclear and confusing since there is no current consensus on this term in nicotine dependence. Most smokers make multiple attempts before achieving success. The issue is further complicated in multinational studies where access to treatments can vary widely from country to country and may be dependent on economic status. In a study of adequate size, randomization across treatment groups can be expected to result in even distribution of subject	Delete sentence: "If in the study……for these groups." **Outcome**: *Patients, who had been treated with other pharmacological treatments but failed, probably will be more treatment resistant to a new agent than naïve subjects. Randomisation, and stratification based on this factor, may prevent bias. The text is adjusted in a way that stratification is recommended, not strictly required, as studies may be large the risk of unbalanced distribution may be low.* **Outcome**: *One could also argue if availability to earlier treatment is related to social-economic status, this is another reason for randomisation, in order to prevent bias due to confounding.*

	characteristics.	
Section 4.1.1 Baseline Characteristics Line 115 Line 121 Line 122	Socio-economic class should be optional; it is unclear how this would translate into labelling. As part of the general health assessment it would be helpful to assess vital signs at baseline as well as body weight Baseline "General Health" score: It is not clear what is intended by the requirement of a "general health score". Since there is no widely established scale for general health it is not clear how any score provided here could be globally interpreted. The health characteristics of the clinical trial population are already defined by the protocol inclusion/exclusion criteria. An arbitrary health score would provide little, if any, additional information of practical use.	**Outcome**: *The guidance has been adapted accordingly.* **Outcome**: *Vital signs are included. Body weight was already included.* **Outcome**: *'General health score' will be changed into 'general health'. , General health score instruments may indeed not be very sensitive or specific.* *However, information about baseline health status should be reported, for evaluation of accordance to the inclusion criteria and safety in the treatment phase.*
Section 4.2 1 Definition of the primary endpoints Lines 126 - 129	Would this be an opportunity to give guidance as to whether strict definitions (e.g. no cigarettes not even a single puff) or the use of more potentially clinically relevant definitions (which recognise the likelihood of the occasional lapse, or take into account the MOA of medications that act to prevent a lapse from becoming a full relapse)?	**Outcome**: *Slips may be allowed shortly after start of treatment, when withdrawal symptoms are most severe, and patients may not be yet stabilized on treatment (e.g. because of titration or boosting). This is called the grace period. However, after the predefined grace period, only subjects who achieve and maintain abstinence for a considerable period (till one year follow-up from randomisation) are considered responders. Patients who start to lapse again after achieving abstinence, are at risk for relapse, and therefore considered as non-responders. Moreover, it could be difficult to distinguish slips from relapse based on biomarkers.*
Section 4.2.1 Definition of the primary endpoints Lines 130-133 (also relates to: Section 4.3.3b, line 192 and Section 4.3.3c, line 204)	Primary endpoint: Lines 128-129 of the guidance state: "its definition should reflect total abstinence for a long enough period of time under treatment". We propose that complete abstinence from smoking during the last 4 weeks of the treatment period is consistent with this. Continued abstinence from smoking after the end of the initial treatment period should be considered absence of relapse after successful cessation. SEE GENERAL COMMENTS The draft guidelines justify the proposed primary endpoint of one year after treatment by referencing a WHO definition of an ex-smoker as one abstinent for at least one year. No reference is provided in the guidelines and there is no readily available	The primary endpoint should be the rate of continuous abstinence (biochemically verified) for the last 4 weeks or the treatment period. **Outcome**: *See response to general comments of EFPIA above for justification.* **Outcome**: *The WHO definition of an ex-smoker is deleted form the text, and justifications for the choice for the primary end-point reflecting 1 year of abstinence are included instead. See introduction*

Line 133	definition of this criterion on the WHO website. Arguably there is a qualitative difference between epidemiological survey and the more rigorous follow-up of a clinical trial. <u>Diaries</u>: While diaries may be considered adequate for assessing smoking status, there are known limitations of this methodology, for example, missing data due to lost diaries or diaries that are backfilled just prior to the clinic visit. Subject self-report in the form of answers to well-defined questions about nicotine/tobacco use has been the norm is smoking cessation trials and is the recommended method according to the 'Russell Standard' criteria (1).	*of this response document for details.* *For reference regarding the WHO-definition of an ex-smoker, see Hughes et al., Nicotine & Tobacco Research 2003;5:13-25.* Also allow self-report based on structured questions **Outcome**: *The guidance is adapted according this proposal.*
Section 4.2.2 Definition of the secondary endpoints		
Line 136	Abstinence at the end of treatment should be primary endpoint. SEE Section 4.2.1 above and GENERAL COMMENTS	**Outcome**: *Not agreed. See response to general comments of EFPIA above for justification of primary endpoint.*
Line 137	Many previous trials have included follow up at 6 months and at 1 year however this has been more typically been from the beginning of therapy rather than the end. Assessing this from the end of therapy becomes more difficult when comparator products are been used which may have a different therapy duration.	Abstinence rate after 12-months should be assessed as secondary endpoint after the 6-month period. **Outcome**: *Not agreed. See response to general comments of EFPIA above for justification of primary endpoint.*
	Long-term data is optimally analyzed with "time-to event" or Kaplan-Meyer survival analyses based on the more efficient and optimal use of all observed data.	Include K-M analyses among secondary endpoints to assess long-term smoking cessation **Outcome**: *Not agreed. See response to general comments of EFPIA above for justification*
Line 140	Other measure of abstinence such as point prevalence should be added as secondary endpoints. Although less stringent than complete abstinence, the point prevalent abstinent population nonetheless represents a group that has made substantial gains compared to baseline levels of smoking.	Add point prevalence abstinence as secondary endpoint. **Outcome**: *Point prevalences are not considered relevant, as these do not reflect sustained abstinence*
	Particularly for new products it is important for safety reasons to assess any change in vital signs as well as just body weight. The latter is not a secondary **efficacy** endpoint.	Change '*Weight change*' to: '*Changes in vital signs and body weight*' and move to safety assessments **Outcome**: *Agreed. Changes in vital signs and body weight' will be added to the safety section.*

Section 4.2.2 Lines 142-149	Requirement of long-term craving data for claim regarding craving: It is an established fact that addiction is associated with complex neural adaptations in reinforcement and reward mechanisms that have become established over lengthy periods (generally many years) of substance abuse. It is unrealistic to consider that a few weeks of treatment can permanently reverse these modifications to the extent that there will be a significant effect many months after the last medication. Moreover, craving is not experienced at constant levels over time, but rather as irregular surges in response to a variety of stimuli. Any assessment of craving in the long-term is confounded by variability in individual circumstances (life style differences, living/associating with smokers) and therefore does not lend itself practically too long-term post-treatment analysis. Analysis is further confounded by the fact that unsuccessful subjects will have returned to smoking and therefore their cravings will be being controlled by cigarette use.	Require subjective nicotine craving and withdrawal data only for treatment period. Assessments immediately post-treatment can evaluate rebound and withdrawal phenomena related to stopping medication
	The corollary, that no claim could be made for an intervention that has a significant effect on craving only during the treatment period, would deny the very real benefit of a treatment that can reduce craving during the period where cessators are at highest risk of relapse. Additionally, the sentence beginning 'Craving feelings usually persist…' is misleading as it could be read as implying that the individual craving feelings persist. 'Usually' is also perhaps too definite.	Craving feelings ~~usually persist~~ ***may occur*** even years after cessation, … **Outcome**: *The section regarding long-term craving data has been deleted. Though it is considered relevant to make a distinction between short-term craving, which is driven by acute withdrawal symptoms, and craving feelings that occur long after acute withdrawal symptoms had disappeared, there is currently no scientific experience how these trials should be performed.*
Lines 150-152, 256)	Distinction should be made between nicotine withdrawal and drug withdrawal. The choice of post treatment assessment should be made with consideration of the PK profile of the product. Assessment immediately after discontinuation may reflect psychological effects of discontinuation whereas pharmacological effect might only be seen when the test drug has substantial cleared from the body (in the case of treatments with longer half lives this might be several days post discontinuation.)	**Outcome**: *As a placebo arm is included, the psychological effects of discontinuation can be estimated and taken into account. Therefore it is considered useful to monitor these symptoms shortly after end-of-treatment. The text is remained as it is.*

Section 4.3 Strategy and Design of Clinical Trials		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**

Section 4.3.1 Pharmacodynamics Lines 155-156	Craving studies are notoriously design-dependent. It is thus not needed to promote it here as proof of concept	Delete first sentence. **Outcome**: *The outcomes of craving studies should indeed be interpreted with care. However, as Phase I proof of concept study craving studies may be relevant. Text is remained.*
Lines 164 - 166	It would be helpful to add an example of where this would not be appropriate, i.e., pharmacological interaction with NRT would not likely occur since the subjects would have been chronically receiving the active ingredient, nicotine (albeit from cigarettes).	**Outcome**: *Even in combined use of chronic NRT, an interaction study is relevant. If NRT is stopped, the induction effect of nicotine on CYP enzymes will disappear. Test is changed into: Smoking and nicotine use may induce CYP enzymes (e.g. CYP1A2, 2A6), and pharmacokinetic interaction studies may be considered if a new drug is metabolised by these enzymes.*
Section 4.3.2 Dose response studies Lines 169-170	We disagree with this statement requiring a parallel fixed-dose design for dose-response studies. Adaptive design in learn phase and in dose-finding studies is highly recommended and should be considered as an option. Adaptive design is an efficient and effective way in proving the concept and in finding the appropriate dose(s) for confirmatory trials. Further, it should be clarified that this is most relevant for new compounds. For existing compounds previously used for another indication, or reformulation of existing compounds, sufficient data may already exist on the appropriate therapeutic range	**Outcome**: *Dose-ranging studies evaluated in a controlled, parallel fixed-dose design, using at least three dosages are preferred. An adaptive design e.g. during the study a dose arm may be discontinued, is acceptable as long as this dose-finding study is exploratory for the confirmatory study* **Outcome**: *the following text is included: For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed.* Proof of Concept studies are described. The next step should be dose ranging, to be followed by confirmatory study(ies). The paragraph under a. Exploratory Trials fully applies to b. Confirmatory Studies. Consider merging the 2 sections.
Line 168 also pertains to lines 172 up to 199	The distinction between exploratory studies and confirmatory studies is not obvious.	**Outcome**: *The major differences between exploratory and confirmatory studies according to the guideline is that confirmatory studies should include an active comparator (this is optional for exploratory studies), and the follow-up may be shorter in exploratory studies. For reasons of clarity, the order of the sections is kept unchanged.*
Section 4.3.3a Exploratory studies Line 180	TQD specification. The TQD requirements described in the draft guidelines ("usually set within two weeks of initiating treatment") are based on current treatment modalities and may limit future creative approaches	Limit TQD description to a suggestion that a TQD should be defined. **Outcome**: *Agreed. This is changed into: Usually a TQD is set within two weeks after initiating treatment though a more prolonged period may be chosen depending on pharmacological*

		properties of the product.
Section 4.3.3b Confirmatory trials Lines 190-196	See GENERAL COMMENTS and Sections 4.2.1, 4.2.2 for comments relating to Primary Endpoint Definition and 'end of therapy'. It is not clear why it is required that active control is used in confirmatory trials. Why cannot one use placebo control to test the efficacy for the treatment of nicotine dependence? Odds Ratios vs placebo provide a comparison of treatment effect across studies. In addition, assuming a confirmatory study uses placebo and active control groups, what is the suggested approach to power the study? What is the recommended comparison between study drug and the active comparator (non-inferiority or superiority)? If non-inferiority is recommended, need to provide guidance regarding how to determine the non-inferiority margin. Should this be 'placebo *and* active controlled trials' or 'placebo *and/or* active controlled trials'? What would be the justification for double dummies being used only for non-oral products?	**Outcome**: *Active controls are needed for regulators to interpret the efficacy and safety of a new treatment option versus a standard treatment. Between study comparisons do not provide valid information in this perspective, as study populations are different and hence their responsiveness.* *In the presence of placebo, non-inferiority of the two active arms may not necessarily need to be proven, although opinions in the EU differ. Two arms non-inferiority studies are not acceptable as it will raise difficulties as the effect size of currently authorized products is rather modest and any loss of efficacy will approach placebo.* **Outcome**: *Text should be interpreted as: confirmatory trials should be three-arm trials including a placebo **and** active-control arm.* **Outcome**: *Double-dummies should indeed be used for oral products as well. Text has been changed accordingly.*
Section 4.3.3c Duration of Treatment Lines 200-204	Why would 1 year off treatment be obligatory to demonstrate maintenance treatment? For most other drug treatments maintenance is used to control symptoms (e.g., high blood pressure, depression, high cholesterol) the effects on maintenance of effect would be investigated whilst on treatment not 12 months after discontinuation of the treatment. Similarly to acute demonstration of efficacy, demonstration of maintenance should be based on on-drug data and not on off-drug data.	**Outcome**: *Text is changed into: For evaluation of an additional benefit of maintenance treatment, the follow-up of at least 6 months off drug is required.* *Most treatment options in treatment of smoking cessation act by modifying acute withdrawal symptoms. For approval of chronic use, it should be justified whether prolonged treatment is indeed useful to prevent relapse once acute withdrawal symptoms have faded away, compared to short term treatment, and whether the effect is sustained longer compared to short-term treatment as well after discontinuation.* **Outcome**: *Both on-drug and off-drug data are considered relevant. For justification see summary of outcome at the end of the document.*

Section 4.3.3d Methodology Lines 209-213	Formal psychotherapy. All currently available pharmacological or behavioural treatments that have "proven efficacy" still have limited response rates. A significant pharmacological treatment effect can be demonstrated over any adjunctive treatment if the latter is provided equally in the placebo arm. The exclusion of "formal psychotherapy with proven efficacy" from pharmacotherapy trials does not allow for potential future combinations of individually effective treatments that may have additive responder rates. Any counselling or psychotherapy should optionally be allowed in clinical trials provided it is administered to all participants as background therapy.	**Outcome**: *Sentence has been deleted in this section. In the confirmatory trials section it is stated that "Any form of therapeutic counselling should be standardised in trials that aim at a primary indication for smoking cessation".*
Section 4.4 Special populations Line 229	Elderly subjects. Requirements for any minimum number of elderly subjects in clinical trials should be specific to the drug under investigation. Where exposure in elderly is within the therapeutic index and there is no effect of age on the exposure response model and there is no reason to suspect sensitivity to the pharmacology in elderly, it should be sufficient to extend the inclusion/exclusion age range to include elderly subjects.	**Outcome**: *A reference to the ICH E7 geriatrics guideline is added to the text.*

COMMENTS FROM : Merck Sharp & Dohme (Europe) Inc.

GENERAL COMMENTS

Section 4.2.1 of Guideline proposes the following for the primary efficacy endpoint: persistent abstinence rate off drug until 1 year after the end of the initial treatment period. We recommend using the abstinence rate off drug until 6 months after end of the initial treatment period. The one year rate could be included as secondary endpoint.

Rationale:

a. based on literature review, the vast majority of relapse happen by 6 months in treatment studies
b. pulmonary function significantly improves by 6 months after abstinence [Buist AS 1979 (reference appended)]
c. 6 months is adequate to assess clinically meaningful efficacy

Outcome:

The endpoint has been adapted in a way that the 1 year period refers to 1 year after randomization instead of 1 year follow-up off drug. The on-drug abstinence period is also considered relevant. As relapse rates are not stabilized after 6 months in the current treatment options, and long-term continuation of abstinence cannot be predicted from short-term results, longer observation periods are required for regulatory purposes. See also summary of outcome to comments on the draft guideline at the end of this document.

We further note that selection of an appropriate comparator for assay validation (or superiority or non-inferiority) may not be feasible for this endpoint, even if a 6-month endpoint is adopted, as currently approved compounds have largely used a 12 week endpoint

Outcome:

Regulatory experience and data from the literature revealed that several products are suitable as active comparators in 12 months trials. Several studies on varenicline, NRT, and bupropion showed that they were superior over placebo after 1 year, even though the studies were not powered for 1 year outcome, and active treatment period was short. If no active comparator will be included, no information about assay sensitivity will be available. This is especially inconvenient if a study on the new product fails.

Section 2 of the Draft guideline indicates that leading principle of guideline is that pharmacotherapy is an aid to become abstinent and remaining abstinent without drug treatment. However, we recommend that the guideline allow consideration of efficacy measured in studies permitting potential intermittent, "booster" or chronic treatment to optimize sustained abstinence.
Rationale:

- addiction is a chronic, relapsing illness
- the vast majority of patients are unable to achieve abstinence with currently available therapy (1-year abstinence rate of 22% varenicline, 16% bupropion SR, 8% placebo [Gonzales JAMA 2006; reference appended)
- efficacious treatment that includes booster/maintenance intervention has clinical utility in that more patients may achieve prolonged abstinence
- benefit/risk of booster/maintenance treatment may have significant clinical advantage over health effects associated with continued chronic nicotine use.

We recommend separating maintenance, and after-treatment phases for efficacy assessment
Rationale:

- Specific mechanism of action of product may be specifically efficacious during acute vs. maintenance phase of treatment
- Recommend allowance for therapeutics that target specific phase of treatment
- Duration of treatment phase must be informed by proposed mechanism of action
- Comparison to active comparator must include appropriate duration of treatment (e.g. 12 weeks when comparator is varenicline)

Outcome: *Maintenance or repeat treatment options are addressed in the guideline section 4.3.3c .*

We recommend that concomitant psychotherapy in confirmatory trials should be adequately described to allow replication in studies and by clinicians
Outcome: *Specific requirements for counselling may hamper feasibility if a new product in clinical practice, especially considering differences in availability of psychotherapeutic support between European member states.*

In addition, a dose ranging study should allow optimization of the dose for each individual patient
Outcome: *The need for individual dose-titration may not apply to every new product, and guidance regarding this issue falls therefore beyond the scope of this document. If the dose would depend on the prior smoking level, the study needs to be randomised for this factor (see section 4.1).*

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION

Line no[1]. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
250	Polycyclic aromatic hydrocarbons from smoke are inducers of CYP1A2, not nicotine. Smoking cessation can abruptly increase the level of drugs metabolized by CYP1A2.	Due to the induction of CYP1A2 isoenzyme by byproducts of cigarette smoke, plasma levels of drugs metabolized by this isoenzyme can increase significantly following smoking cessation. **Outcome:** *agreed. Similar wording is included in section 4.3.1: "Smoking and nicotine use may induce CYP enzymes (e.g. CYP1A2, 2A6), and pharmacokinetic interaction studies may be considered if a new drug is*

[1] Where available

		metabolised by these enzymes."

COMMENTS FROM JOHNSON & JOHNSON CONSUMER GROUP (JJCG)

GENERAL COMMENTS

Summary of comments

Johnson & Johnson Consumer Group (JJCG) and its legacy companies has been researching and developing treatments for tobacco dependence for more than 30 years. Nicorette® Gum, the first pharmacotherapy to effectively aid smoking cessation, was first marketed by JJCG in 1978. Since then, JJCG has developed and marketed new nicotine replacement products, and we have a significant ongoing commitment to research and development in this area. The clinical development group at JJCG has extensive expertise in conducting clinical studies. More than 100 randomised, controlled trials (ranging from phase I to phase IV) of new treatments for tobacco dependence, involving more than 30,000 smokers have been performed by JJCG, and the trial results have been published in peer-reviewed papers.

The efficacy and safety of nicotine replacement therapy (NRT) are well established. More than 100 published clinical trials (efficacy trials with long-term follow up), including more than 40 000 smokers in total, have shown that NRT effectively aids smoking cessation, and NRT is the most widely used treatment for tobacco dependence (Silagy et al 2004). There is extensive data, from both published papers and post-marketing surveillance, which shows that NRT products are well tolerated within established dose ranges. The safety of all Nicorette® nicotine replacement products (chewing gum, transdermal patch, nasal spray, inhaler, sublingual tablets and lozenges) is regularly monitored, and the data summarized in Periodic Safety Update Reports. Post-marketing experience with Nicorette® products shows that the reported adverse events are very rare events relative to the billions of units that have been used by smokers attempting to quit. The data does not indicate any potential for long-term adverse events. Overall, no important risk data has been identified from the clinical studies or the extensive post-marketing surveillance.

Johnson & Johnson Consumer Group seeks to collaborate with governments, regulatory authorities, and healthcare organizations to establish and promote guidelines and policies that encourage wider access to proven therapies, and further develop effective products for smoking cessation treatment. Johnson & Johnson Consumer Group welcomes the initiative to develop guidelines that would increase innovation and access to treatments. However, in their current form we believe the draft guideline would have a negative impact in terms of innovation, development of new forms of existing treatments such as NRT, and access, thereby decreasing the number of new treatments available to smokers in the future. The draft guideline also puts EMEA at odds with national and international organisations; the World Health Organization Framework Convention on Tobacco Control, World Bank, and UK Royal College of Physicians all encourage greater access to effective treatment, whereas the EMEA guideline would reduce access and counteract the development of new and better NRT formulations.

The current draft guideline appears to have been motivated by the need to develop guidelines for new smoking cessation products, such as nicotine conjugate antigens, which are completely different from existing pharmacotherapies. In their current form, the draft guideline does a disservice to existing pharmacotherapies. For example, mandatory requirement to demonstrate the long-term efficacy of a novel NRT product in clinical trials - when current data already supports the efficacy of all existing NRT formulations – represents a barrier to further development of such clinically-proven treatments.

Another concern relates to suggestions for clinical trial design for all treatment, including NRT, namely the mandatory need for active and placebo control in phase III confirmatory studies. This would considerably increase the sample size needed in the studies, the complexity and the cost. It is also questionable what this approach would add for NRT products. Comparison to active controls could be used in a second step to support specific new claims but should not be considered mandatory in the first phase if not applicable for specified reasons.

In our view, the draft guideline is focusing on the development of new chemical entities within the smoking cessation area and we therefore encourage the

committee to e revise and rewrite the guideline so that it is fully comprehensive, including NRT in a separate subsection with relevant guidelines for this specific group of products. If this is not possible, the focus of the guideline should be limited to new chemical entities, but exclude replacement drugs with long post-marketing records, such as NRT.

Scope and content of guideline

The title, scope and content of the draft guideline are confusing in several respects. The executive summary states that the aim of the guideline is "to provide guidance in the development of clinical studies…." Regarding the intended scope of the document, it is stated that "several treatment modalities, such as NRT….are available, others are within the scope of development". This, and other content, implies that the scope of the guideline document does not relate to available therapies. In addition, clearer definition of terms is required – there is currently confusion between "new products" (new formulations of existing drugs) and new chemical entities (NCEs).

It is also notable that 'nicotine conjugate antigens' are mentioned repeatedly throughout the text. It appears that the primary purpose of this document is to address the unique characteristics of such treatments, which will involve more extensive testing than existing tobacco dependence treatments. As such, perhaps the guideline should focus on nicotine vaccines and other NCEs and not constrain innovation in nicotine replacement therapy (NRT) by requiring more data than necessary.

However, if the guideline is going to apply to both existing and new treatments for tobacco dependence, the current draft would significantly constrain development of NRT products such as those with novel routes of administration or improved delivery characteristics. The draft guideline puts NRT on the same level as NCEs, without taking into consideration the enormous amount of published data supporting the safety and efficacy of NRT. NRT is a unique therapy for the treatment of tobacco dependence that cannot be compared to NCEs that have recently been introduced or are currently in development. Therefore, should there be intent for the scope of the guideline to include NRT, Johnson & Johnson Consumer Group propose insertion of a sub-section of the guideline that specifically addresses NRT (see below), on the grounds that the data on the safety and efficacy of NRT have consistently been documented over 30 years, and NRT has been in clinical use for a similar period of time. Extensive NRT experience should allow applications to be submitted under the "well-established use" criteria according to Article 10a of Directive 2001/83/EC, making it possible to replace results of pharmacological, toxicological and clinical trials by reference to published scientific literature. This contrasts with an NCE or vaccine, which should follow the guideline in order to provide adequate clinical documentation of safety and efficacy.

We also note that the entire guideline document focuses on the effects of nicotine, and not on the primary causes of smoking-related disease, which are the combustion components of tobacco smoke.

Separate subsection on NRT

If the guideline is to include NRT, Johnson & Johnson Consumer Group would like to take this opportunity to initiate discussion with the appropriate regulatory bodies regarding a revised and more simplistic approach for future NRT clinical development programs, to be harmonized within the EU region and integrated in future NRT guidelines.

Current situation

Nicotine replacement products have been on the market for almost 30 years. Numerous data are available to support the safety and efficacious use of these products within the established dose ranges. All the commercially available forms of NRT (chewing gum, transdermal patch, nasal spray, inhaler, sublingual tablets and lozenges) are effective as part of a strategy to promote smoking cessation. They increase the odds of quitting approximately 1.5 to 2-fold compared to placebo (Silagy et al 2004). NRT products can be broadly divided into two categories – transdermal delivery, and buccal/oral delivery. The modes of action and pharmacokinetic profiles of products within each of these categories are quite similar and very well known.

In order to gain approval for new NRT products many regulatory agencies currently require either stand-alone safety and efficacy documentation (phase III trials), or evidence of strict bio-equivalence (BE) between the new product and a relevant comparator. However, there appears to be little scientific value in

enrolling a large number of patients into studies of treatments for which much data already exists; and this would also prolong the development of new products. In addition, it is also sometimes a challenge to obtain strictly defined BE, even for similar products, and for a product that is replacing self-titrating smoking, strict BE is not the relevant measurement in all cases. On this basis, it could therefore be argued that new registrations of NRT products within the currently approved dose range could be based on existing clinical data, without jeopardizing the future safety of any consumer. Applications submitted under the "well-established use criteria according to Article 10a of Directive 2001/83/EC referring to published or known clinical data should be accepted.

Establishment of a bracketing regulatory strategy for NRT products

We propose the establishment of a "safety and efficacy window" based on the "strength" and "speed of onset" of currently approved and well-known NRT products.

For example, analysis of pharmacokinetic (PK) parameters valid for current oral Nicorette nicotine replacement formulations (i.e. 2 mg and 4 mg sublingual tablets, 2 mg and 4 mg chewing gum and 10 mg oral inhaler) shows that the levels for $AUC_{10\ min}$, which can be used as a measurement of speed of nicotine delivery, ranges between approximately 10-30 ng/ml x min. Similarly, AUC_{inf}, which is a measure of exposure, ranges between about 15-35 ng/ml x h. If a new NRT product has PK characteristics that fall within the above limits (i.e. within the range of other NRT products with previously documented safety and efficacy), there should not be any need to further document the clinical efficacy and safety of the new product for regulatory purposes.

One cornerstone of the clinical rationale for accepting bracketing is that individuals who use flexible-dose NRT self-titrate their nicotine dose, in the same way that smokers do when they use tobacco. Since the dosing of NRT over a full day results in considerable inter-individual variation, conventional single-dose pharmacokinetic characteristics do not provide an accurate picture. It is also important to take into consideration the plasma nicotine levels obtained over the course of a day; it is safe to assume that the nicotine levels obtained would be similar, irrespective of NRT source. It is therefore logical that if a new NRT product falls within the boundaries of previously well-documented and approved NRT products with respect to safety and efficacy, the new product should not have to be separately characterized. For example, a new nicotine 3 mg oral dosage form should only have to document that its PK profile falls within the range of other approved products, in this case, for example, nicotine 2 mg and 4 mg gums (i.e. data on single-dose PK, multiple-dose PK and plasma nicotine levels during ad libitum use should be presented in a regulatory submission). But there would be no need to perform any additional clinical phase III studies, even though it would
not be possible to demonstrate bio-equivalence between the 3 mg and either 2 mg or 4 mg doses. Again, the obvious must be emphasized: smokers using oral nicotine formulations know how to avoid "over-dosing" as the consequence is nausea, a rather similar situation to when they smoke "too much". Nicotine is not a new entity for smokers, but something they know very well how to control.

In summary, the establishment of a bracketing strategy would permit faster and effective approval of new NRT products based on range(s) of efficacy/safety, offering smokers more treatment options to use when trying to quit without jeopardizing the future safety of any consumer. A PK profile should always be documented for any new NRT product.

Phase III clinical trials

For a new NRT product that shows a more aggressive PK profile (i.e. faster uptake of nicotine, or higher plasma nicotine levels, than currently approved products), the safety profile does need to be confirmed in phase III studies. If, on the other hand, the new product shows a slower and/or lower nicotine uptake than current NRT therapies, it should be sufficient to demonstrate abstinence results in phase III cessation trials after a maximum of 3 months of treatment, in comparison with placebo.

In addition to abrupt cessation, the use of NRT for 'reduce to stop' (facilitating smoking cessation after a period of smoking reduction in smokers not motivated to quit abruptly) also needs to be considered, as this indication is approved in a number of European countries. The optimal duration of treatment in clinical studies of NRT for reduction to stop remains to be finally agreed.

In future efficacy trials of smoking cessation and/or reduction to stop with new NRTs for registration purposes, the study population should be healthy smoking volunteers, who are either motivated and willing to stop smoking abruptly, or willing to reduce smoking with NRT as the first step to completely quitting

smoking. Johnson & Johnson Consumer Group would welcome discussion on the definition of the smoking population interested in quitting. For example, the smoking population could be regarded as one - admittedly heterogeneous - group, with differing needs for actions and standards: smokers ready to quit abruptly should be encouraged to do so, while smokers not ready or able to quit immediately should be advised to use NRT to cut down smoking as much as possible before making the quit attempt. These two subpopulations could be studied in the same clinical trial, with the primary clinical endpoint being point prevalence abstinence or sustained abstinence after a defined time period, e.g., 3-6 months or 4-6 months. The final broader indication, which would be a combination of the current smoking cessation and reduction to stop indications, would simplify the message to smokers, and result in less complicated clinical programs, which would shorten the time to access of new and better smoking cessation treatments.

Use of shorter outcome measures in clinical efficacy trials

As NRT treatments have been studied extensively during the past 30 years, there is sufficient knowledge to extrapolate long-term abstinence rates from short-term treatment results. A recent publication on this subject by treatment experts concluded that: “A robust index of effectiveness of a course of treatment is the increase in the proportion of smokers who achieve at least 6 months of continuous abstinence” (West et al 2005). Experts also conclude that: “The reason for adopting this index is that our estimates of health gains from stopping smoking are based mainly on permanent cessation versus continued smoking, and 6 months of continuous abstinence provides sufficient information to make reliable estimates of permanent cessation.” (West 2007). More specifically, a longer follow-up to 1 year, as suggested in the EMEA draft guideline, is usually not a primary endpoint in current practice (Hughes et al 2003). Most adverse events occur in the early phase of NRT treatment, i.e. during the first 3-4 weeks. Longer follow-up times than 6 months and further safety evaluations should be part of phase IV, i.e. post-marketing activities.

In summary, it is well-known that results obtained at earlier stages, e.g., at 3-6 months, are generally very consistent with results obtained at longer term follow-ups, i.e. 12 months or longer. In fact, important differences in efficacy can be detected earlier (i.e. within the first two months of treatment).

Comparator for novel NRTs

Comparing the efficacy and safety of new NRT products with existing products is not really relevant when the real comparator, the cigarette, delivers significantly higher levels of nicotine. Cigarettes are widely available to the public with limited control of effect and safety, or manufacturing control. Since NRT acts by replacing some of the nicotine from cigarettes one could argue that cigarettes should be considered as comparators, and that the normal risk:benefit rationale and demand for clinical evidence when increasing a dose above the existing benchmark is not directly applicable to NRT. Increasing the dose of nicotine from NRT to a level that is still below the dose from cigarettes would give a more efficacious NRT product. For new higher strength NRT products, clinical guidelines should focus on safety aspects rather than the need to document efficacy. The same applies to novel NRT products with faster speed of onset; the focus should be on safety and the comparator in the form of cigarettes should be taken into consideration.

Conflict between draft guideline and expert opinion

Experts in the treatment of tobacco dependence products (i.e. the Society for Research on Nicotine and Tobacco, the World Health Organization, the UK Royal College of Physicians) are calling for stronger, faster-acting, NRT products (RCP 2000; WHO 2001). They also want regulatory requirements for NRT to be relaxed and reduced, in order to facilitate development of novel NRT products and widen access to existing NRT products (McNeill et al 2001; RCP 2007). But new guidelines that will prolong the clinical development programmes and significantly increase the burden of clinical evidence will have the opposite effect, by slowing the development and introduction of new NRT treatments.

For example, the recommendation for longer follow-up times in phase III studies - up to 12 months after last dose – does not reflect current standards in trials of tobacco dependence treatments. The current standard for evaluation is 1 month (28-day) abstinence (the United States FDA definition: identified as the window between weeks 2 and 6 of treatment), justified since data show that short-term outcomes correlate well with longer-term outcome and most subjects who relapse do so within the first few days/weeks of quitting. If clinical trials are to be powered to demonstrate significant difference between new treatment and control at 1 year, study cohorts would need to be very large due to high dropout rate in cessation studies. The large study population and long follow up time would make studies very costly. This is a barrier to the development of any new treatments, at the very time tobacco control experts are pressing for new products to be developed and the regulatory barriers for treatments to be lowered, because the alternative will always be the high risk of continuing smoking.

Another disparity between the draft guideline and expert opinion is the reasoning around craving measurements, which is not in agreement with what other treatment experts have concluded and recommended. For example, the suggestion to study effects on craving long after treatment has ended bears no scientific meaning.

Outcome: *The focus of the "Guideline on the Development of Medicinal Products for the Treatment of Smoking" is indeed on new substances including 'nicotine-conjugate vaccins'. Whether new efficacy studies are needed for line extensions of established products will depend on the claim and data available. In principle, references could be made to earlier studies. If higher plasma levels are aimed, additional safety data might be needed. The following text is included:*
4.3.1: "For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed."

For comments on long-term follow-up and craving, see comments below and summary of outcome to comments on the draft guideline at the end of this document.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no[2]. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Title	The recognised disease, listed in the WHO *International Statistical Classification of Diseases* (ICD-10, item F17.2), is tobacco dependence (not nicotine dependence). The term 'tobacco dependence' is routinely used by WHO, and WHO has guidelines relating to treatment of tobacco dependence at EU and Global levels. National guidelines, where they exist, also routinely reference tobacco dependence e.g. the United States Clinical Practice Guideline on *Treating Tobacco Use And Dependence.*	Amend title to 'Guideline on the development of medicinal products for the treatment of tobacco dependence' **Outcome:** *Indeed, tobacco dependence is the preferred term by the WHO and ICD-10. However, it has been decided that the title 'treatment of smoking' would cover more clearly the intended indication.*
Lines 33-34	Carbon oxide should be carbon monoxide.	Change 'carbon oxide' to 'carbon monoxide' **Outcome:** *Agreed. Changes are made accordingly.*
Lines 33-34	Regarding toxicity, more emphasis should be put on the non-nicotine components in tobacco and tobacco smoke, which are the primary causative factors of smoking-related death and disease.	**Outcome:** *Agreed. The following text is added to section 1, Introduction: "Tobacco toxicity is mainly due to smoke compounds (carcinogens like polycyclic aromates) and combustion products like carbon monoxide."*
Line 38	The global smoking prevalence figures do not add valuable	**Outcome:** *European data are added. Detailed data about epidemiology of*

[2] Where available

	information.	*smoking are not considered of major importance for this guidance document on development of new products for treatment of smoking.*
Line 41	When describing epidemiology, the accepted term is 'smoking' rather than 'nicotine dependence'	Change 'Nicotine dependence is…' to 'Smoking is…' **Outcome:** *The term 'nicotine dependence' has been replaced by smoking in the epidemiology section.*
Paragraph 1.2	Perhaps NRT & bupropion should be listed as established treatments, with varenicline in a separate paragraph as an example of newer treatments.	**Outcome:** *The term "established treatment" actually refers to products that are registered in Europe as an aid to stop smoking. Any categorisation based on registration period would not be appropriate.*
Lines 50-52	There is no explanation of how NRT works (whereas the mechanism of action of bupropion is explained in lines 52-55).	Add explanation of mechanism of action of NRT. **Outcome:** *it is decided that detailed information regarding established products are beyond the scope of this document, and information about bupropion has been deleted. There is therefore no need to discuss the mechanism of NRT in detail in this guideline.*
Line 50	Varenicline should be mentioned as a pharmacotherapeutic intervention	…NRT, bupropion, and varenicline **Outcome:** *agreed*
Line 51	Sublingual tablet is missing.	Add sublingual tablet **Outcome:** *Point not taken. This section is not meant to discuss all established treatment option in detail. The term 'e.g.' before the row of different NRT formulations indicates that this summary is not complete.*
Line 55	As the mechanism of action of bupropion is explained, the mechanism of action of varenicline should also be added	Add explanation of mechanism of action of varenicline. **Outcome:** *See outcome line 50-52 above.*
Lines 56-58	This is not an appropriate forum to discuss comparative efficacy of different treatments. The aim of this guideline is to 'provide guidance in the development of clinical studies for the treatment of tobacco dependence'. Discussion of comparative efficacies of treatments should be undertaken by experts in systematic reviews, such as the Cochrane Collaboration.	Delete these lines. **Outcome:** *Agreed. These lines have been deleted.*
Line 56	More details should be given of the established efficacy of all licensed NRT products. See: Silagy et al 2004 and NICE 2002. In summary, NRT is the standard pharmacological treatment for tobacco dependence, its effect is well-proven, and the products are very well tolerated.	Add details on established efficacy of NRT. **Outcome:** *Point not taken. This would not be in line with comments to line 56-58, i.e. that this guideline is not an appropriate forum to discuss comparative efficacy of different treatments.*
Lines 59-61	More explanation should be given over choice of treatment. NRT and bupropion are singled out for contraindications, but NRT is not contraindicated in patients with stable cardiovascular	Describe the safety of NRT products more accurately. **Outcome:** *See outcome of line 56*

	disease. France and UK, for example, have deleted all contraindications for NRT in patients with cardiovascular disease. The tolerability of NRT should be more accurately described. There is no mention that varenicline is a new treatment that has yet to be tested in special groups. There is also no mention of the tolerability of varenicline. A recent research report describes the safety profiles of NRT vs varenicline in a routine care setting in a smoking cessation clinic. The report shows a" higher incidence of adverse drug symptoms among those taking varenicline" (Stapleton et al 2007).	Describe the known safety profile of varenicline in more detail. **Outcome:** *See outcome of line 56*
Lines 66-68	NRT is not contraindicated in any of the patient groups mentioned.	Delete sentence. **Outcome:** *This is a point of debate. In some member states of the EMEA, NRT is contraindicated for unstable cardiovascular patients. Specific contraindications are now removed from the text, as this document is not meant as a treatment-guidance.*
Lines 69-70	The comment re 'development of alternative pharmacotherapies' reinforces the impression that this guideline is primarily aimed at NCEs, not existing drugs used to aid cessation.	**Outcome:** *The focus of the "Guideline on the Development of Medicinal Products for the Treatment of Smoking" is indeed new substances including 'nicotine-conjugate vaccins'. The following text is included:* *4.3.1: "For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed."*
Line 73	Again, the reference to "new products" that will be developed (as opposed to the "development of products so far") implies that the guideline is intended to address entities other than NRT, varenicline & bupropion. 'New products' need to be clearly defined.	**Outcome:** *See outcome above, line 69-70*
Lines 74-75	" an aid to become abstinent" implies 'reduce to stop' (facilitating smoking cessation after a period of smoking reduction in smokers not motivated to quit abruptly). Nicorette Gum and/or Inhaler have been approved for 'reduce to stop' in a number of European countries, including Austria, Belgium, Czech Republic, Denmark, France, Germany, Iceland, Italy, Latvia, Netherlands, Spain, Sweden, Switzerland, and the UK. 'Reduce to stop' is identified in addition to " an aid to "remaining abstinent" This is a welcome distinction, although greater clarification would be helpful.	**Outcome:** *The following text is included in the scope section: "Smoking reduction is not considered an indication target. The benefit of smoking reduction on health outcome is debatable. A more gradual 'cut-down to quit' approach may be applied in the clinical trials in patients not able or willing to quit abruptly, but abstinence is still considered as the ultimate treatment goal and hence the primary outcome should reflect abstinence.´* *See also summary of outcome, section "Smoking reduction as an intermediate treatment goal" at the end of this document, for further justification.*
Line 80	'Smoking reduction' may be confused with reduce to stop (a gradual reduction in smoking, leading to complete cessation)	Change to 'Smoking reduction without quitting as the ultimate objective is not…'

		Outcome: *See outcome Line 74-5 above*
Line 105-106	DSM-IV-TR or ICD-10 criteria are not normally used as entry criteria in clinical trials with NRT.	**Outcome:** *Agreed. The following inclusion criterion is now defined in the guideline: "Smokers with the intention to quit smoking" (see section 4.1, Subject characteristics and selection of subjects)*
Line 108	We are not aware of the routine of stratifying smokers into naïve vs "treatment resistant smokers" – this is not common practice.	**Outcome**: *It can not be excluded that patients, who had been treated with other pharmacological treatments but failed, might be more treatment resistant to the new drug than naïve subjects. Randomisation based on this factor could prevent bias.* *New text: "The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. In principle, inclusion should be as broad as possible. Subjects may be stratified according to their level of nicotine dependence, or the earlier use of other pharmacological treatments."*
Line 119	The FTND score is not the only preferred measurement of dependence	Delete "by the FTND" **Outcome:** *Agreed. Text has been adapted as follows: "the level of dependence measured by the FTND or another validated instrument" (Section 4.1.1 Baseline characeristics)*
Line 120	"amount of craving"	Change to: "level of craving" **Outcome:** *Not agreed. The term 'amount of craving' is used in the literature. (E.g. Reuter & Hennig, Human Psychopharmacology 2003; 18: 437-46)*
Line 122	'General health score' should be specified / clarified. Phase II and III studies include healthy smokers and subgroups of patients with co-morbidities are not included in these phases. This is part of phase IV programs or extended program when applicable. Having to include co-morbidities as well would extensively increase study samples and study complexity.	**Outcome:** *Health status is not meant as a randomisation factor. Baseline information regarding health is however needed for interpretation of safety data. Has been changed into: "The following descriptive features at least should be documented: general health, vital signs (e.g. blood pressure), body weight." (see section 4.1.1, Baseline characteristics)*
Line 132	'Persistent abstinence' is not generally used to describe abstinence. Preferable to use one of the previous definitions, such as sustained abstinence or point prevalence abstinence, for consistency.	4.2.1 Definition of the primary endpoints **Outcome:** *In smoking cessation studies so far, different definitions have been used to express abstinence (e.g. continuous abstinence, total abstinence, sustained abstinence, prolonged abstinence etc). Different terms may be used for defining the primary outcome, though its definition should reflect continuous abstinence rate without slips or episodes of relapse to smoking throughout the follow-up period. (See 4.2.1, Definition of the primary endpoints)*
Line 132	The recommendations of long follow-up times in phase III	**Outcome:** *There is no strong evidence that short term efficacy as short as*

	studies - up to 12 months after last dose – would result in unnecessarily long clinical studies. There is good evidence to support 1-month abstinence as the outcome measure, as there is a strong correlation between short-term and long-term outcomes.	*1 month would indeed predict long-term efficacy. Especially for new treatment options like vaccines, with a prolonged half-life compared to established products, the maintenance of effect might be different than reported in the past for NRT.*
Lines 132-133	Measuring abstinence at a specified timepoint 'after the end of the initial treatment period' is not ideal, as the interpretation of this may differ. Abstinence can be measured either from the date treatment commences, or from quit date, which is the accepted standard. We are not aware of any evidence to suggest that there are problems with the existing standard (measurement of abstinence from quit date).	**Outcome**: *The requirement of 1 year abstinence from end-of-treatment has been changed. Now the active treatment period can be taken into account in the assessment of efficacy. Starting point of evaluating efficacy may be Target Quit Data and/or end of the 'grace period', a period in the initial phase of active treatment where slips are allowed. The off-drug period should be taken into account as well, as relapse tend to increase after drug withdrawal, and only sustained abstinence over a considerable period is considered clinical relevant.*
Line 134	Carbon oxide should be carbon monoxide.	Change to 'carbon oxide' to 'carbon monoxide' **Outcome**: *agreed. Text is adapted accordingly.*
Line 136	Abstinence rate at the end of treatment is considered as a primary endpoint.	**Outcome**: *See outcome Line 132-3 above*
Line 137	"after end of treatment"	Change to: "after start of treatment" **Outcome**: *See outcome Line 132-3 above*
Lines 141	'Health outcome' needs to be defined.	**Outcome**: *changed into: general health, vital signs (e.g. blood pressure), body weight*
Line 142	Vivid dreams and sleep disorders are not a nicotine withdrawal symptom	Change to "insomnia" **Outcome**: *Agreed. Vivid dreams should be reported as psychiatric side effect rather than withdrawal symptom. Text has been changed accordingly.*
Line 144	Wisconsin and Minnesota scale names are incorrect.	Change to correct names: Wisconsin Smoking Withdrawal Scale, the Minnesota Nicotine Withdrawal Scale, and add the correct references. **Outcome**: *agreed. Text is adapted accordingly.*
Line 144	American Psychiatric Association DSM can also be used, as well as ICD-10	Add DSM-IV-TR **Outcome**: *A reference to DSM-IV-TR is added to the list.*
Line 144-146	The names of the scales should be cited correctly.	**Outcome**: *See outcome Line 144 above*
Lines 145 – 152	The reasoning around craving measurements is not in agreement with what other treatment experts have concluded and recommended. Measuring the effect on craving 1 year after end of treatment is unrealistic. No treatment, if not administered for	Short-term data is sufficient for specific claims regarding craving. **Outcome**: *The role of craving in long-term relapse is indeed not clarified. The text is revised as follows: "Measuring withdrawal symptoms and*

	chronic use, could present this kind of long-term efficacy.	*craving is not only of interest during active treatment, but also in the period immediate after the subjects will become off-drug. This should be taken into account in the study design." (see Section 4.2.2, Definition of secondary endpoints.*
Line 148	Any parameters should be measured at a defined timepoint from the start of treatment (not 'after treatment' which is too vague)	Change 'after treatment' to 'after start of treatment' **Outcome**: *More specific guidance when craving should be assessed is now given in Section 4.2.2. See outcome Lines 145-52 above.*
Line 156	Discontinuing NRT is not associated with withdrawal symptoms.	Change 'withdrawal of nicotine' to 'withdrawal symptoms after abstinence from smoking' **Outcome**: *Not agreed. The short-term withdrawal symptoms of smoking are mainly determined by nicotine withdrawal.*
Line 190	Randomised studies do not need to include placebo as well as active control. This would result in unrealistic study sample sizes.	Change 'placebo and active' to 'placebo or active', when considered appropriate'. **Outcome**: *Three-arm studies were applied in the pivotal trials of both varenicline and bupropion, indicating feasibility. If no active comparator will be included, information about assay sensitivity will be lacking. This will be especially inconvenient if a study on the new product fails.*
Line 192 & Line 204	1 year off drug is not the same as 1 year after the end of the initial treatment period. Outcome should be measured from the start of treatment.	**Outcome**: *It cannot be expected that therapeutic effect is optimal from the very first dose. The primary outcome should be measured from the point where the patient is stabilised, after a predefined 'grace period'. See Section 4.2.1 of the final version for details.*
Line 209 and 221	It is not correct to refer to "nicotine dependence"	Change to: "tobacco dependence" **Outcome**: *Not agreed, as the term nicotine dependence is widely accepted in the field (e.g. Fagerström Test for Nicotine Dependence).*
Lines 219-225	Draft guideline states that pharmacokinetic and safety data are required if adolescents are included in the labelling. This may be relevant for NCEs but many published studies in which NRT has been used in adolescents reported no safety problems. The current licensing in the UK allows NRT use in 12-17 year olds.	**Outcome**: *Extrapolation to adult data is complicated; adolescents may be less motivated to stop smoking, which may affect efficacy outcomes.* *As this guideline is not meant to provide treatment guidance, NRT for adolescents is not discussed.*
Lines 260-262	Amend sentence 'Nicotine withdrawal symptoms…..(validated) tools' "Compensatory smoking" seems to be present here specifically for vaccines, this should be made clear.	Change to: 'Nicotine withdrawal symptoms may be separated from craving symptoms and measured with different (validated) tools, or combined, with craving being an item on the withdrawal scale.' **Outcome**: *A reference to section 4.2.2 has been added for further clarification.* **Outcome**: *Compensatory smoking is also mentioned under 4.5.2 Specific adverse events, Nicotine-conjugate antigens*

References lines 272-273	Citation details for American Psychiatric Association DSM-IV are incorrect	Change to: American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text revision (DSM-IV). Washington DC: American Psychiatric Association, 2000. **Outcome**: *Given the widespread use DSM-IV-TR, the reference as given is considered sufficiently clear.*

COMMENTS FROM Dr. Peter Hajek

GENERAL COMMENTS

Although there are a number of good and useful points made, the document also contains mistakes and omissions.

Essential issues such as validation of smoking status, intention-to-treat analysis, handling of drop-outs, 'protocol violators', 'treatment non-responders' etc. are not considered. There are statements which are incorrect, and suggestions which are of unclear value.

EMEA should consider consulting existing guidelines such as the Russell Standard (West, R. et al. (2005) Outcome criteria in smoking cessation trials: the need for a common standard. Addiction, 100, 299-303). As the EMEA document will impact the future progress in this important field, a wider range of experts should be involved in its development.

References

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Stapleton JA, Watson L, Spirling LI, Smith R, Milbrandt A, Ratcliffe M, Sutherland G. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. *Addiction,* published online November 2007; doi:10.1111/j.1360-0443.2007.02083.x.

West R. The clinical significance of 'small' effects of smoking cessation treatments Addiction 2007; 102: 506–509.

West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005; 100: 299–303.

World Health Organization. Regulation of nicotine replacement therapies: an expert consensus. World Health Organization Regional Office for Europe: Copenhagen, 2001.

Outcome: *This guidance on product for the treatment of smoking should be envisioned in connection with other, more general ICH and EMEA guidelines on methodological issues and statistics. Issues like the definition of the ITT population, handling of drop-outs, protocol-violators etc. are therefore not discussed in detail in this guidance. In section 3, LEGAL BASIS, some references to relevant guidelines are given. A definition of responder is given in Section 4.2.1, Definition of the primary endpoints.*

Furthermore, the proposal for standardisation of outcomes from the field and the other references mentioned by Prof Hajek were considered as very relevant,

and several publications are taken into account in the EMEA guideline. Regulatory objectives may be different however than purely scientific ones. The main objective of the EMEA guidance is to provide a framework for development of new products, in order to obtain evidence that a new product is efficacious, and the benefits outweigh the risks. The EMEA guidance is not intended as clinical practice guideline. Different endpoints (i.e. continuous abstinence till follow-up of 1 year) and study designs (active comparator) are therefore proposed in this regulatory guideline than in some other publications. See also summary of outcome to comments on the draft guideline below for further justification.

COMMENTS FROM THE ASSOCIATION OF THE EUROPEAN SELF-MEDICATION INDUSTRY (AESGP)

GENERAL COMMENTS

AESGP represents the manufacturers of non-prescription medicines in Europe.

Despite the overall prevalence of tobacco dependence falling, Datamonitor estimates that tobacco dependence still affects nearly 116m individuals across the seven major markets. We welcome, therefore, this initiative to develop a guideline that helps manufacturers to develop new therapies for the treatment of tobacco dependence.

AESGP member companies, as manufacturers involved in developing treatments for tobacco dependence for more than 30 years, have a great deal of experience and understanding of tobacco dependence. These companies would welcome the opportunity to work with the EMEA to refine and develop this draft guideline further. They would also like the opportunity to comment on the guideline again prior to finalisation.

AESGP strongly supports the better regulation principles, particularly that regulatory requirements should be proportionate to risk. In this instance we note that the draft guideline appears to have been written to help develop new and novel smoking cessation products such as nicotine conjugate antigens. These are very different from existing pharmacotherapies such as Nicotine Replacement Therapies (NRT), the efficacy and safety of NRT are well established and there is extensive data from both published papers and post-marketing surveillance. We submit, therefore, that applications for new NRT products should be based on bibliographic data or bioequivalence data and that clinical development of new NRT products should only be required for products falling outside the known limits for NRT. In view of this, we would like to propose that the guideline either excludes NRT altogether or is amended so that it is comprehensive and covers all therapies for tobacco dependence. If the intention is to include all therapies for tobacco dependence we would propose the guideline is amended to incorporate specific sections for the different types of products/developments, for example as indicated below for new chemical entities (NCEs) /vaccines and established products:

Type of product / development	**Evidence required**
NCEs and vaccines	Full clinical development programme required
Existing compounds outside current limits / range	Some safety data required – development based on extension of existing efficacy and safety. No need to repeat toxicity studies
Existing compounds within current limits e.g. flavour change	Bibliographic

We would like to request that the terminology throughout the guideline is clear and consistent e.g. nicotine dependence and tobacco dependence are not synonymous / interchangeable. NCE may not be the correct terminology as not all products will be “chemical”, ‘new medical products’ may be a more suitable term to include both pharmacological and biological entities.

We would also suggest the guideline is made shorter and that extraneous material is removed to make it more focused. For example we do not think it is appropriate to detail the review of mechanism of action, safety and efficacy of established treatments for tobacco dependence in a clinical development guideline.

Outcome: The general comments made by the AESGP are largely supported, and are implemented in the text (see 'Specific comments on the text' below). However, the AESGP proposal for a detailed schedule of the regulatory pathway for applications of new products is beyond the scope of this guideline. There are several general regulatory guidelines applicable, and the scope of the guideline is rather scientific than purely regulatory.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Title	The title of any guidance document is very important as it serves as the initial signpost on relevance for people seeking further information about a particular subject. The current title is rather confusing; we suggest that the term 'tobacco dependence' is used rather than 'nicotine dependence'. The guideline provides guidance around clinical trials (efficacy and safety) and not product development. We would like to suggest revising the title to:' Guideline on the clinical development of (new)* medicinal products for the treatment of tobacco dependence' or 'Guideline on the development of safety and efficacy data for (new)* medicinal products for the treatment of tobacco dependence * The word "new" may need to be included in the title depending on the agreed scope of the guideline (i.e. whether existing products are deemed to be in or out of scope)	'Guideline on the clinical** development of new medicinal products for the treatment of tobacco dependence' or 'Guideline on the development of safety and efficacy data for new* medicinal products for the treatment of tobacco dependence' * May need to include "new" in title depending on the scope of the guideline (if existing products in or out of scope) **Please note that "clinical" would need to be defined so as to exclude PK data. **Outcome**: *The title is changed into: "Guideline on the Development of Medicinal Products for the Treatment of Smoking". Although smoking is largely driven by nicotine dependence, its harm is mainly caused by combuststion products of tobacco rather than nicotine dependence. Therefore, treatment of smoking is considered a more adequate term. Dependence to NRT is no target indication. See also response to comments made by Johnson & Johnson Consumer Group on this issue.*
1. Introduction	Please see General Comments above We do not believe it is the role of a guideline to include general information or comments about relative efficacy, or mechanisms of action	• Delete sections 1 & 1.1 and replace with one sentence describing the 3 "categories" of products as described in the table in the general comments section • Section 1.2 – retain lines 48 – 52 Delete from "Bupropion was originally …" to end of line 61. • Retain lines 62 – 66 up to" years." Delete remainder of 66 to end of 68 • Retain lines 69 & 70

		• Insert sentence that safety and efficacy of existing treatment is established. • Section 1.2 prefer use of term 'existing approved treatments' or 'approved treatments' to 'established treatments'. **Outcome:** *Agreed. Such a review is more relevant for treatment guidelines. The text about established treatment options is considerably shortened and no comparisons regarding efficacy are made (see section 1.2). A more general statement is included: Individual preference and tolerability determines whether one or the other product will be used.*
2. Scope	See General Comments The scope of the guideline should be clarified and the distinction between NCEs/vaccines and existing CEs needs to be emphasised. As currently drafted the guideline assumes abrupt cessation and does not envisage a situation where products may be used continuously over an extended period of time (chronic usage products). The effect of this is that the draft guideline appears to prevent the development of products for long term / continuous use. The guideline focuses on NCEs and vaccines. In our view the requirements contained therein are not appropriate for and shouldn't cover existing products (NRT etc) unless the development in question falls outside of the currently approved therapeutic range and in this event the requirement should be limited to the submission of extensions of existing data *(See comments & table above)*.Clarification of terminology is required e.g. what is meant by a "new product"? We propose a definition – see General Comments	• Line 75, remove 'without drug treatment' and add 'from tobacco use' **Outcome:** *This document –as usual in EMEA guidelines for specific diseases and medical conditions- is indeed mainly intended as guidance for development of new active compounds. The following is added for clarification on this point:* *4.3.1.: For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed.* **Outcome:** *Maintenance therapy is not discouraged in the guideline, but the benefit of long-term (or even life-long) maintenance therapy needs to be established. Specific guidance on the evaluation of maintenance therapy is given in section 4.3.3.c of the final guidance text.* *If feasible, short-term 'curative' treatment options are still preferred, for safety and compliance reasons. Therefore, the text has been adapted as follows: "The leading principle for the present guideline is that pharmacotherapy is an aid to become abstinent and remaining abstinent, preferably without drug treatment."* • Delete remainder of section **Outcome:** *See comment to Line 75, ahead of this column* **Outcome:** *this term is explained in more detail later on in the text by definition of the primary endpoint (see section 4.2.1 of final guideline text). Harm reduction is currently not considered as a valid indication.. See for further motivation on harm reduction 'CHMP Summary of Outcome to Comments' at the end of this document.*

	Line 75 – "remaining abstinent" should be defined.	
3. Legal Basis	The list of relevant legal and regulatory documents, is dependent on and, will need to be checked and verified for accuracy when the scope of guideline is finalised	• Article 10(a) and bioequivalence guidelines should be included if the scope of the guideline includes all categories of products **Outcome:** *In section 3 of this guideline, a reference is made to EMEA guidance document "Pharmacokinetic studies in man'. In this document, a reference is made to bioavailability and bioequivalence guideline. No further reference is thus needed.*
4.1 Subject characteristics and selection of subjects	The terminology used in line 105 is confused and requires clarification as terms may not be synonymous or used interchangeably without affecting the sense of the document (smoking & tobacco use, nicotine and tobacco dependence) Previous treatment experiences and levels of dependence could be noted but formal stratification would apply too onerous a burden on trial design. Access to treatments can vary widely from country to country and may be dependent on economic status. To stratify for these could therefore be difficult, especially in multinational studies. Also such stratification would be contaminated by these factors as 'naivety' to previous treatments may be as much influenced by lack of access as lack of desire. There is not generally accepted stratification of dependence so doing this may result in a diversity of approaches (e.g. different FTND scores or cigarettes per day across studies). Formal stratification adds complexity to trial design and increases costs and timing and as such could hinder the stated desire to encourage the development of alternative pharmacological therapies (Section 1.2 Line 70)	• Change 'nicotine dependence' to 'tobacco dependence' **Outcome** (line 105): *Agreed. Text is reworded: 'Smokers with the intention to quit smoking are eligible.'* • Remove references to stratification. **Outcome**: *Patients, who had been treated with other pharmacological treatments but failed, probably will be more treatment resistant to a new agent than naïve subjects. Randomisation, and stratification based on this factor, may prevent bias. The text is adjusted in a way that stratification is recommended, not strictly required. As studies may be large the risk of unbalanced distribution may be low.* *New text: <u>The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. In principle, inclusion should be as broad as possible. Subjects may be stratified according to their level of nicotine dependence, or the earlier use of other pharmacological treatments.</u>* line 114 onwards • Include level of motivation **Outcome:** *The list is meant as minimal requirement for essential data that need to be noted at baseline, as these data are expected to be relevant in the evaluation of the final efficacy and safety outcomes.* *It is acknowledged that level of motivation might have some impact on efficacy. However, level of motivation is not considered as an essential baseline item that should be included per se, as only smokers with the intention to stop smoking (thus being motivated) will be included in the main studies (see section 4.1, subject characteristics & inclusion criteria). The level of motivation is thus not expected to form a significant factor in a population selected on this criterion. Moreover, specific labelling for non-motivated smokers won't be acceptable.* *But of course, Investigators are free to extent the baseline characteristics if it*

		thought to be relevant (e.g. in special populations such as adolescents). • Change body weight to vital signs and body weight in 4.1.1 **Outcome**: *Agreed. Vital signs and body weight are added to the list of baseline characteristics.*
Section 4.2	This section lists various methods of measuring abstinence but provides no guidance as to which one to use. Clarification is required as to whether they are all equally valid and/or any one could be chosen. The guideline could provide an opportunity to give guidance as to whether strict definitions (e.g. no cigarettes not even a single puff) should be used or the use of more potentially clinically relevant definitions which recognise the likelihood of the occasional lapse.	• Add vital signs to 4.2.2 and words to effect ' These secondary endpoints could be considered' **Outcome:** *Based on recommendations of other parties, vital signs has been removed from the list of secondary outcomes, as it is rather a safety outcome.* *In principle, all these secondary endpoints should be addressed in the dossier.The choice for secondary endpoints has been based on earlier regulatory experience with dossiers of products in the treatment of smoking. Though the final decision will be based on the primary endpoint, these secondary endpoints are considered helpful to get more insight in pattern of response (response at en-of-treatment and after 6 months) and properties of the drug regarding treatment of withdrawal symptoms and craving. For reasons of harmonisation and to ease comparison between earlier dossiers, some standardisation is proposed. It is not expected that these outcomes will be difficult to measure.* **Outcome**: *For the primary outcome, a more strict definition is proposed. A responder is considered a subject who achieves continuous abstinence without slips for a considerable follow-up period (1 year). For further justification of the choice of the endpoint and trial duration see 'CHMP Summary of Outcome to Comments' at the end of this document.* • Measuring cravings a year after treatment is irrelevant – delete 'long term data' in line 148 – only short term data needed if going to make a claim about craving. **Outcome**: *Agreed. Text has been changes accordingly.* • Line 142 – list needs to be checked – discrepancies with DSM 4 **Outcome**: *Agreed. Has been changed into: ' irritability, depression, restlessness, insomnia, difficulty concentrating, and increased appetite"* • Line 142 - Craving needs to be included in list of symptoms – suggest sentence starts 'Craving and ….' **Outcome**: *as modification of craving by treatment may be a key factor in relapse prevention, craving is discussed separately from other the symptoms of smoking cessation.*

		• Line 148 delete and long term (eg 1 year after treatment) **Outcome**: *Agreed. Text has been changes accordingly.* • Line 151 change should to could **Outcome**: *Not agreed. Measuring craving and withdrawal symptoms when the patient becomes off-drug is considered relevant in the evaluation whether gradual down-tapering is needed or not.*
	The guidance provided needs to be cognizant of and preferably consistent with other requirements globally particularly FDA, to avoid duplication of studies	**Outcome**: *The FDA has no guidance for smoking indication to date, and therefore it is impossible to harmonise requirements in this research area. This EMEA guideline complies to general ICH guidance documents on trials, which are also valid for FDA applications.*
	The most appropriate time to assess the *efficacy* of a pharmacological treatment is at the end of the treatment period and therefore this should be the primary endpoint for efficacy. To explore efficacy several weeks or months after treatment has been discontinued, is unhelpful in assessing the efficacy of a drug for a chronic relapsing condition such as nicotine dependence as other unspecified events may have occurred to influence behaviour (e.g., peer pressure, environmental stimuli etc.) It is extremely rare for the efficacy of drugs for the treatment of other chronic relapsing conditions (e.g. high blood pressure, asthma, and high cholesterol, depression) to be assessed long after treatment has been discontinued. Additionally, the design and powering of studies with an endpoint at 1 year after initial treatment would make studies extremely large, costly and time consuming and as such could hinder the stated desire to encourage the development of alternative pharmacological therapies (Section 1.2 Line 70). Follow-up after treatment discontinuation can however be an important index of *effectiveness* and follow up at 6 months and 1 year is important in this regard as a secondary endpoints. This enables an assessment of whether a relatively permanent behaviour change has been achieved by a comparatively short term therapy	**Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies.*

	As stated in Section 1.2 Lines 62-63 despite current treatment options '…many people remain having difficulty with becoming abstinent and especially remaining abstinent over time' therefore it is important to be open to treatments that might, for some patients, manage the condition (in the way, many blood pressure and cholesterol treatments do) rather than completely eradicate the condition (as is generally speaking the aim of existing therapies).	**Outcome**: *Harm reduction is not considered as a valid endpoint. See: 'CHMP Summary of Outcome to Comments' at the very end of this document for justification.*
	Additionally a primary outcome such a long period off treatment would raise the issue of how should failures be dealt with? For example a subject could be considered a failure at the end of the trial but then subsequently stops smoking – does this rate as success? Also how long should the time point be?	**Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies.*
	We would recommend that the guideline encourages keeping subjects in a study as long as possible even if they are failing at a particular time point, i.e. they should not necessarily be discontinued at their first lapse, however this recommendation should be optional not mandatory.	**Outcome:** *This recommendation would be rather redundant, as it is generally required for trials that non-responders or drop-outs should be followed-up , according to intention to treat principle (i.e. subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment). A reference to ICH-E9, where this principle is laid down, is included in this NfG on development of products for treatment of smoking.*
	Section 4.2.2 – secondary end points may be useful but shouldn't be mandatory – could be an unnecessary burden. Particularly for new products it is important for safety reasons to assess any change in vital signs as well as just body weight. The latter is not a secondary efficacy endpoint. Health outcomes can provide valuable information on effectiveness; however, some of the current tools are imprecise and add complexity to studies. In many studies, particularly in early phases of development it may not be meaningful to collect health outcome data. This secondary outcome should either be deleted or made optional for use when appropriate	**Outcome:** *agreed, health outcome and body weight are deleted as secondary outcome.*
	Line 150 – Is the guideline referring to rebound symptoms? This should be clarified. The choice of post	**Outcome:** *Both rebound and withdrawal symptoms to the drug may occur. How to assess rebound and withdrawal symptoms has been further explored in the safety section (see section 4.5.2). This is covered by the sentence "These phenomena should be regularly monitored for a substantial amount of time after discontinuation of the drug." in section 4.5.2*

	treatment assessment should be made with consideration of the PK profile of the product. Assessment immediately after discontinuation may reflect psychological effects of discontinuation whereas pharmacological effect might only be seen when the test drug has substantially cleared from the body (in the case of treatments with longer half lives this might be several days post discontinuation.).	**Outcome:** *In principle, psychological effects of the ending of treatment could be distinguished from withdrawal of pharmacological effect as a placebo arm will be included in the confirmatory studies*
Section 4.3	Line 190 Should this be 'placebo *and* active controlled trials' or 'placebo *and/or* active controlled trials' Line 191 What would be the justification for double dummies being used only for non-oral products? Double dummy trials should apply more widely than non-oral - suggest rephrasing to say double dummies could be applied (should be if blind study) See previous comment about obligation to follow up for 1 year. Why would 1 year off treatment be obligatory to demonstrate maintenance treatment? For most other drug treatments maintenance is used to control symptoms (e.g., high blood pressure, depression, high cholesterol)	• Line 155 – 170 – going back to very early development – not relevant to a clinical development guideline – suggest deletion of sections 4.3.1 and 4.3.2 **Outcome**: *The AESGP proposes to delete the sections regarding PK-PD and dose-finding studies. This not agreed. As these data form the basis of the dose and design of Phase II-III (exploratory and confirmatory) studies, some guidance related to specific features of treatment of smoking has been provided in the document.* • Line 190 – confirmatory trials – should be 'and/or' – should not be obliged to do both **Outcome**: *Active controls are needed for regulators to interpret the efficacy and safety of a new treatment option versus a standard treatment. Between study comparisons do not provide valid information in this perspective, as study populations are different and hence their responsiveness.* *In the presence of placebo, non-inferiority of the two active arms may not necessarily need to be proven, although opinions in the EU differ. Two arms non-inferiority studies are not acceptable as it will raise difficulties as the effect size of currently authorized products is rather modest and any loss of efficacy will approach placebo.* • Line 190 delete non oral **Outcome:** Agreed, but instead of deletion the sentence is rephrased by: "For new oral or non-oral products double dummies could be applied." • Line 196 amend to …cessation and reported. • Duration of treatment – should be maintenance of effect – drug only works while being used. Suggest deletion of second part of line 203 and line 204 **Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies.*

	the effects on maintenance of effect would be investigated whilst on treatment not 12 months after discontinuation of the treatment. The guideline is silent on the presentation of results – Section 4.2.1 would benefit from inclusion of additional information on this point. Behavioural support should be standardized and reported Lines 207 – 213 – the section is unclear and requires clarification or deletion. It seems to be referring to behavioural support. Special populations – Would be useful to include definitions of 'children', 'adolescents' and 'elderly'. These definitions should be aligned to definitions elsewhere e.g. FDA Psychiatric co-morbidity – Not necessary for NRT but safety profile needed for NCE / new drugs and special precautions in use Suggest inclusion of other co-morbidities associated with smoking – need data before can claim use in these special populations.	**Outcome:** *Section 4.2.1 (regarding primary outcome) is extended to clarify how the primary endpoint should be substantiated and measured..* **Outcome:** *Agreed, the following phrase has been included: 'Any form of therapeutic counselling should be standardised in trials that aim at a primary indication for smoking cessation' (see Section 4.3.3b).* **Outcome:** *Agreed, line 207-13 are deleted.* **Outcome:** *The FDA and EMEA share definitions of age bounderies in ICH guidelines. In section 3 of this report, references are made to ICH guidelines on elderly and paediatric populations (ICH E7 (elderly) & E11 (paediatrics)).* **Outcome:** *as the guideline refers to development of new compounds, no further specifications regarding the use of established treatment options in psychiatric patients are necessary to add.* *From a regulatory perspective, not efficacy, but rather tolerability data are relevant for special populations like COPD and cardiac patients. Efficacy will be evaluated in the main study population. Specific indications based on co-morbidities (e.g. 'smokers with COPD) are not acceptable. See also outcomes regarding comments made by SEPAR (Smoking Prevention Group of the Spanish Respiratory Society) on this issue (line 234 and section 4.4).*
Section 4.5	4.5.2 – not relevant to look for drug interactions for NRT because users already taking nicotine during smoking – would be needed for NCE's. Line 259 - This should be clarified. The choice of post treatment assessment should be made with consideration of the PK profile of the product. Assessment immediately after discontinuation may reflect psychological effects of discontinuation whereas pharmacological effect might only be seen when the test drug has substantially cleared from the body (in the case of treatments with longer half lives this might be several days post discontinuation.)	**Outcome:** *It is already stated in section 4.3.1.that ' For line extensions of established products like NRT, reference may be made to earlier studies'. This also apply for PK and PD interactions.* **Outcome**: *See answer above line 150*

	Line 262 – Where appropriate, compensatory smoking should be assessed. The guideline is silent on the combination use of NRT with other treatments for tobacco dependence and also on the possibility of an adjunctive therapy approach being taken – these should be included.	**Outcome:** *In principle, compensatory smoking should be evaluated for all new active compounds. It is not expected that this would be a large effort, as number of cigarettes will be anyway be registered in non-responders. Based on their pharmaceutical action, compensatory smoking might be specifically relevant for vaccines. Compensatory smoking is therefore also mentioned under 4.5.2 Specific adverse events, Nicotine-conjugate antigens* **Outcome:** *For the registration of a new drug, the proof of concept and benefit-risk balance of the new compound needs to be evaluated. Preferably, this is done for monotherapy, as the efficacy and safety profile of the drug alone could than be estimated without bias of co-treatments.* *Add-on studies with e.g NRT can be submitted as supportive studies, and is considered as relevant information for treatment guidelines, but cannot be required from a regulatory point of view.*

COMMENTS FROM The Proprietary Association of Great Britain, (J & J Consumer Group, GSK Consumer Healthcare and Novartis Consumer Health)

GENERAL COMMENTS

The Proprietary Association of Great Britain, PAGB, is the UK national trade association for over the counter medicines and food supplements. We represent the major manufacturers of these products in the UK, (J & J Consumer Group, GSK Consumer Healthcare and Novartis Consumer Health). This response represents the views of PAGB and its members. PAGB works closely with government, regulators, health professionals and patients representative organisations to establish and promote policies that encourage wider access to proven therapies that have been shown to benefit public health. Despite the overall prevalence of tobacco dependence falling, Datamonitor estimates that tobacco dependence still affects nearly 116m individuals across the seven major markets. We welcome, therefore, this initiative to develop a guideline that helps manufacturers to develop new therapies for the treatment of tobacco dependence.

PAGB member companies, as manufacturers involved in developing treatments for tobacco dependence for more than 30 years, have a great deal of experience and understanding of tobacco dependence. These companies would welcome the opportunity to work with the EMEA to refine and develop this draft guideline further. They would also like the opportunity to comment on the guideline again prior to finalisation.

PAGB strongly supports the better regulation principles, particularly that regulatory requirements should be proportionate to risk. In this instance we note that the draft guideline appears to have been written to help develop new and novel smoking cessation products such as nicotine conjugate antigens which are very different from existing pharmacotherapies such as Nicotine Replacement Therapies (NRT). The efficacy and safety of NRT are well established and there is extensive data from both published papers and post-marketing surveillance. We submit, therefore, that applications for new NRT products should be based on bibliographic data or bioequivalence data and that clinical development of new NRT products should only be required for products falling outside the known limits for NRT. In view of this PAGB and its member companies would like to propose that the guideline either excludes NRT altogether or is amended so that it is comprehensive and covers all therapies for tobacco dependence. If the intention is to include all therapies for tobacco dependence we would propose the guideline is amended to incorporate specific sections for the different types of products/developments, for example as indicated below for new chemical entities (NCEs) /vaccines and established products:-

Type of product / development	**Evidence required**
NCEs and vaccines	Full clinical development programme required
Existing compounds outside current limits / range	Some safety data required – development based on extension of existing efficacy and safety. No need to repeat toxicity studies
Existing compounds within current limits e.g. flavour change	Bibliographic

We would like to request that the terminology throughout the guideline is clear and consistent e.g. nicotine dependence and tobacco dependence are not synonymous / interchangeable. NCE may not be the correct terminology as not all products will be “chemical”, new medical products may be a more suitable term to include both pharmacological and biological entities.

We would also suggest the guideline is made shorter and that extraneous material is removed to make it more focused. For example we do not think it is appropriate to detail the review of mechanism of action, safety and efficacy of established treatments for tobacco dependence in a clinical development guideline.

Outcome: *The general comments made by the PAGB are largely supported, and are implemented in the text (see ‘Specific comments on the text’ below). However, the PAGB’s proposal for a detailed schedule of the regulatory pathway for applications of new products is beyond the scope of this guideline. There are several general regulatory guidelines applicable, and the scope of the guideline is rather scientific than purely regulatory.*

GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Title	The title of any guidance document is very important as it serves as the initial signpost on relevance for people seeking further information about a particular subject. The current title is rather confusing; we suggest that the term 'tobacco dependence' is used rather than 'nicotine dependence'. The guideline provides guidance around clinical trials (efficacy and safety) and not product development. We would like to suggest revising the title to:' *Guideline on the clinical development of (new)* medicinal products for the treatment of tobacco dependence'* or *'Guideline on the development of safety and efficacy data for (new)* medicinal products for the treatment of tobacco dependence* * The word "new" may need to be included in the title depending on the agreed scope of the guideline (i.e. whether existing products are deemed to be in or out of scope)	*'Guideline on the clinical** development of new medicinal products for the treatment of tobacco dependence'* or *'Guideline on the development of safety and efficacy data for new* medicinal products for the treatment of tobacco dependence'* * May need to include "new" in title depending on the scope of the guideline (if existing products in or out of scope) **Please note that "clinical" would need to be defined so as to exclude PK data. **Outcome:** *The title is changed into: "Guideline on the Development of Medicinal Products for the Treatment of Smoking". Although smoking is largely driven by nicotine dependence, its harm is mainly caused by combuststion products of tobacco rather than nicotine dependence. Therefore, treatment of smoking is considered a more adequate term. Dependence to NRT is no target indication. See also response to comments made by Johnson & Johnson Consumer Group on this issue.*
1. Introduction	Please see General Comments above We do not believe it is the role of a guideline to include general information or comments about relative efficacy, or mechanisms of action	• Delete sections 1 & 1.1 and replace with one sentence describing the 3 "categories" of products as described in the table in the general comments section • Section 1.2 – retain lines 48 – 52 Delete from "Bupropion was originally …" to end of line 61. • Retain lines 62 – 66 up to" years." Delete remainder of 66 to end of 68 • Retain lines 69 & 70 • Insert sentence that safety and efficacy of existing treatment is established. • Section 1.2 prefer use of term 'existing approved treatments' or 'approved treatments' to 'established treatments'. **Outcome:** *Agreed. Such a review is more relevant for treatment guidelines. The text about established treatment options is considerably shortened and no comparisons regarding efficacy are made (see section 1.2). A more general statement is included: Individual preference and tolerability determines*

		whether one or the other product will be used.
2. Scope	See General Comments The scope of the guideline should be clarified and the distinction between NCEs/vaccines and existing CEs needs to be emphasized. As currently drafted the guideline assumes abrupt cessation and does not envisage a situation where products may be used continuously over an extended period of time (chronic usage products). The effect of this that the draft guideline appears to prevent the development of products for long term / continuous use. The guideline focuses on NCEs and vaccines. In our view the requirements contained therein are not appropriate for and shouldn't cover existing products (NRT etc) unless the development in question falls outside of the currently approved therapeutic range and in this event the requirement should be limited to the submission of extensions of existing data *(See comments & table above).* Clarification of terminology is required e.g. what is meant by a "new product"? We propose a definition – see General Comments Line 75 – "remaining abstinent" should be defined.	• Line 75, remove 'without drug treatment' and add 'from tobacco use' **Outcome:** *This document –as usual in EMEA guidelines for specific diseases and medical conditions- is indeed mainly intended as guidance for development of new active compounds. The following is added for clarification on this point:* *4.3.1.: For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed.* **Outcome:** *Maintenance therapy is not discouraged in the guideline, but the benefit of long-term (or even life-long) maintenance therapy needs to be established. Specific guidance on the evaluation of maintenance therapy is given in section 4.3.3.c of the final guidance text.* *If feasible, short-term 'curative' treatment options are still preferred, for safety and compliance reasons. Therefore, the text has been adapted as follows: "The leading principle for the present guideline is that pharmacotherapy is an aid to become abstinent and remaining abstinent, preferably without drug treatment."* • Delete remainder of section **Outcome:** *See comment to Line 75, ahead of this column* **Outcome:** *this term is explained in more detail later on in the text by definition of the primary endpoint (see section 4.2.1 of final guideline text). Harm reduction is currently not considered as a valid indication.. See for further motivation on harm reduction 'CHMP Summary of Outcome to Comments' at the end of this document.*
3. Legal Basis	The list of relevant legal and regulatory documents, is dependent on and, will need to be checked and verified for accuracy when the scope of guideline is finalised	• Article 10(a) and bioequivalence guidelines should be included if the scope of the guideline includes all categories of products **Outcome:** *In section 3 of this guideline, a reference is made to EMEA guidance document "Pharmacokinetic studies in man'. In this document, a reference is made to bioavailability and bioequivalence guideline. No further reference is thus needed.*
4.1 Subject characteristics	The terminology used in line 105 is confused and requires clarification as terms may not be synonymous or used	• Change 'nicotine dependence' to 'tobacco dependence' **Outcome** (line 105): *Agreed. Text is reworded: 'Smokers with the intention to*

and selection of subjects	interchangeably without affecting the sense of the document (smoking & tobacco use, nicotine and tobacco dependence) Previous treatment experiences and levels of dependence could be noted but formal stratification would apply too onerous a burden on trial design. Access to treatments can vary widely from country to country and may be dependent on economic status. To stratify for these could therefore be difficult, especially in multinational studies. Also such stratification would be contaminated by these factors as 'naivety' to previous treatments may be as much influenced by lack of access as lack of desire. There is not generally accepted stratification of dependence so doing this may result in a diversity of approaches (e.g. different FTND scores or cigarettes per day across studies) Formal stratification adds complexity to trial design and increases costs and timing and as such could hinder the stated desire to encourage the development of alternative pharmacological therapies (Section 1.2 Line 70)	*quit smoking are eligible.'* • Remove references to stratification. **Outcome**: *Patients, who had been treated with other pharmacological treatments but failed, probably will be more treatment resistant to a new agent than naïve subjects. Randomisation, and stratification based on this factor, may prevent bias. The text is adjusted in a way that stratification is recommended, not strictly required. As studies may be large the risk of unbalanced distribution may be low.* *New text: <u>The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. In principle, inclusion should be as broad as possible. Subjects may be stratified according to their level of nicotine dependence, or the earlier use of other pharmacological treatments.</u>* line 114 onwards 3 Include level of motivation **Outcome:** *The list is meant as minimal requirement for essential data that need to be noted at baseline, as these data are expected to be relevant in the evaluation of the final efficacy and safety outcomes.* *It is acknowledged that level of motivation might have some impact on efficacy. However, level of motivation is not considered as an essential baseline item that should be included per se, as only smokers with the intention to stop smoking (thus being motivated) will be included in the main studies (see section 4.1, subject characteristics & inclusion criteria). The level of motivation is thus not expected to form a significant factor in a population selected on this criterion. Moreover, specific labelling for non-motivated smokers won't be acceptable.* *But of course, Investigators are free to extent the baseline characteristics if it thought to be relevant (e.g. in special populations such as adolescents).* Change body weight to vital signs and body weight in 4.1.1 **Outcome**: *Agreed. Vital signs and body weight are added to the list of baseline characteristics.*
Section 4.2	This section lists various methods of measuring abstinence but provides no guidance as to which one to use. Clarification is required as to whether they are all equally	• Add vital signs to 4.2.2 and words to effect ' These secondary endpoints could be considered' **Outcome:** *Based on recommendations of other parties, vital signs has been removed from the list of secondary outcomes, as it is rather a safety outcome.*

	valid and/or any one could be chosen. The guideline could provide an opportunity to give guidance as to whether strict definitions (e.g. no cigarettes not even a single puff) should be used or the use of more potentially clinically relevant definitions which recognise the likelihood of the occasional lapse. The guidance provided needs to be cognizant of and preferably consistent with other requirements globally particularly FDA, to avoid duplication of studies	*In principle, all these secondary endpoints should be addressed in the dossier.The choice for secondary endpoints has been based on earlier regulatory experience with dossiers of products in the treatment of smoking. Though the final decision will be based on the primary endpoint, these secondary endpoints are considered helpful to get more insight in pattern of response (response at en-of-treatment and after 6 months) and properties of the drug regarding treatment of withdrawal symptoms and craving. For reasons of harmonisation and to ease comparison between earlier dossiers, some standardisation is proposed. It is not expected that these outcomes will be difficult to measure.* **Outcome**: *For the primary outcome, a more strict definition is proposed. A responder is considered a subject who achieves continuous abstinence without slips for a considerable follow-up period (1 year). For further justification of the choice of the endpoint and trial duration see 'CHMP Summary of Outcome to Comments' at the end of this document.* • Measuring cravings a year after treatment is irrelevant – delete 'long term data' in line 148 – only short term data needed if going to make a claim about craving. **Outcome**: *Agreed.* • Line 142 – list needs to be checked – discrepancies with DSM 4 **Outcome**: *Agreed. Has been changed into: ' irritability, depression, restlessness, insomnia, difficulty concentrating, and increased appetite"* • • Line 142 - Craving needs to be included in list of symptoms – suggest sentence starts 'Craving and ….' **Outcome**: *as modification of craving by treatment may be a key factor in relapse prevention, craving is discussed separately from other the symptoms of smoking cessation.* • Line 148 delete and long term (eg 1 year after treatment) **Outcome**: *Agreed.* • Line 151 change should to could **Outcome**: *Not agreed. Measuring craving and withdrawal symptoms when the patient becomes off-drug is considered relevant in the evaluation whether gradual down-tapering is needed or not.* **Outcome**: *The FDA has no guidance for smoking indication to date, and therefore it is impossible to harmonise requirements in this research area. This*

	The most appropriate time to assess the *efficacy* of a pharmacological treatment is at the end of the treatment period and therefore this should be the primary endpoint for efficacy. To explore efficacy several weeks or months after treatment has been discontinued, is unhelpful in assessing the efficacy of a drug for a chronic relapsing condition such as nicotine dependence as other unspecified events may have occurred to influence behaviour (e.g., peer pressure, environmental stimuli etc.) It is extremely rare for the efficacy of drugs for the treatment of other chronic relapsing conditions (e.g. high blood pressure, asthma, and high cholesterol, depression) to be assessed long after treatment has been discontinued. Additionally, the design and powering of studies with an endpoint at 1 year after initial treatment would make studies extremely large, costly and time consuming and as such could hinder the stated desire to encourage the development of alternative pharmacological therapies (Section 1.2 Line 70). Follow-up after treatment discontinuation can however be an important index of *effectiveness* and follow up at 6 months and 1 year is important in this regard as a secondary endpoints. This enables an assessment of whether a relatively permanent behaviour change has been achieved by a comparatively short term therapy As stated in Section 1.2 Lines 62-63 despite current treatment options '…many people remain having difficulty with becoming abstinent and especially remaining abstinent over time' therefore it is important to be open to treatments that might, for some patients, manage the condition (in the way, many blood pressure and cholesterol treatments do) rather than completely eradicate the condition (as is generally speaking the aim of existing therapies). Additionally a primary outcome such a long period off treatment would raise the issue of how should failures be	*EMEA guideline complies to general ICH guidance documents on trials, which are also valid for FDA applications.* **Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies* **Outcome**: *Harm reduction is not considered as a valid endpoint. See: 'CHMP Summary of Outcome to Comments' at the very end of this document for justification.* **Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies.*

	dealt with? For example a subject could be considered a failure at the end of the trial but then subsequently stops smoking – does this rate as success? Also how long should the time point be?	
	We would recommend that the guideline encourages keeping subjects in a study as long as possible even if they are failing at a particular time point, i.e. they should not necessarily be discontinued at their first lapse, however this recommendation should be optional not mandatory.	**Outcome:** *This recommendation would be rather redundant, as it is generally required for trials that non-responders or drop-outs should be followed-up , according to intention to treat principle (i.e. subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment). A reference to ICH-E9, where this principle is laid down, is included in this NfG on development of products for treatment of smoking.*
	Section 4.2.2 – secondary end points may be useful but shouldn't be mandatory – could be an unnecessary burden. Particularly for new products it is important for safety reasons to assess any change in vital signs as well as just body weight. The latter is not a secondary efficacy endpoint	**Outcome:** *agreed, health outcome and body weight are deleted as secondary outcome.*
	Health outcomes can provide valuable information on effectiveness; however, some of the current tools are imprecise and add complexity to studies. In many studies, particularly in early phases of development it may not be meaningful to collect health outcome data. This secondary outcome should either be deleted or made optional for use when appropriate	
	Line 150 – Is the guideline referring to rebound symptoms? This should be clarified. The choice of post treatment assessment should be made with consideration of the PK profile of the product.	***Outcome:*** *Both rebound and withdrawal symptoms to the drug may occur. How to assess rebound and withdrawal symptoms has been further explored in the safety section (see section 4.5.2). This is covered by the sentence "These phenomena should be regularly monitored for a substantial amount of time after discontinuation of the drug." in section 4.5.2*
	Assessment immediately after discontinuation may reflect psychological effects of discontinuation whereas pharmacological effect might only be seen when the test drug has substantially cleared from the body (in the case of treatments with longer half lives this might be several days post discontinuation.)	***Outcome:*** *In principle, psychological effects of the ending of treatment could be distinguished from withdrawal of pharmacological effect as a placebo arm will be included in the confirmatory studies*

Section 4.3		• Line 155 – 170 – going back to very early development – not relevant to a clinical development guideline – suggest deletion of sections 4.3.1 and 4.3.2 **Outcome**: *The PAGB proposes to delete the sections regarding PK-PD and dose-finding studies. This not agreed. As these data form the basis of the dose and design of Phase II-III (exploratory and confirmatory) studies, some guidance related to specific features of treatment of smoking has been provided in the document.*
	Line 190 Should this be 'placebo *and* active controlled trials' or 'placebo *and/or* active controlled trials'?	• Line 190 – confirmatory trials – should be 'and/or' – should not be obliged to do both **Outcome**: *Active controls are needed for regulators to interpret the efficacy and safety of a new treatment option versus a standard treatment. Between study comparisons do not provide valid information in this perspective, as study populations are different and hence their responsiveness.* *In the presence of placebo, non-inferiority of the two active arms may not necessarily need to be proven, although opinions in the EU differ. Two arms non-inferiority studies are not acceptable as it will raise difficulties as the effect size of currently authorized products is rather modest and any loss of efficacy will approach placebo.*
	Line 191 What would be the justification for double dummies being used only for non-oral products? Double dummy trials should apply more widely than non-oral - suggest rephrasing to say double dummies could be applied (should be if blind study)	• Line 190 delete non oral **Outcome:** Agreed, but instead of deletion the sentence is rephrased by: "For new oral or non-oral products double dummies could be applied."
	See previous comment about obligation to follow up for 1 year.	• Line 196 amend to …cessation and reported.
	Why would 1 year off treatment be obligatory to demonstrate maintenance treatment? For most other drug treatments maintenance is used to control symptoms (e.g., high blood pressure, depression, high cholesterol) the effects on maintenance of effect would be investigated whilst on treatment not 12 months after discontinuation of the treatment.	• Duration of treatment – should be maintenance of effect – drug only works while being used. Suggest deletion of second part of line 203 and line 204 **Outcome**: *See: 'CHMP Summary of Outcome to Comments' at the end of this document for justification of the requirement of 1 year studies.*
	The guideline is silent on the presentation of results – Section 4.2.1 would benefit from inclusion of additional information on this point.	**Outcome:** *Section 4.2.1 (regarding primary outcome) is extended to clarify how the primary endpoint should be substantiated and measured..*
	Behavioural support should be standardized and reported	**Outcome:** *Agreed, the following phrase has been included: 'Any form of therapeutic counselling should be standardised in trials that aim at a primary indication for smoking cessation' (see Section 4.3.3b).*

	Lines 207 – 213 – the section is unclear and requires clarification or deletion. It seems to be referring to behavioural support. Special populations – Would be useful to include definitions of 'children', 'adolescents' and 'elderly'. These definitions should be aligned to definitions elsewhere e.g. FDA Psychiatric co-morbidity – Not necessary for NRT but safety profile needed for NCE / new drugs and special precautions in use Suggest inclusion of other co-morbidities associated with smoking – need data before can claim use in these special populations.	**Outcome:** *Agreed, line 207-13 are deleted.* **Outcome:** *The FDA and EMEA share definitions of age bounderies in ICH guidelines. In section 3 of this report, references are made to ICH guidelines on elderly and paediatric populations (ICH E7 (elderly) & E11 (paediatrics)).* **Outcome:** *as the guideline refers to development of new compounds, no further specifications regarding the use of established treatment options in psychiatric patients are necessary to add.* *From a regulatory perspective, not efficacy, but rather tolerability data are relevant for special populations like COPD and cardiac patients. Efficacy will be evaluated in the main study population. Specific indications based on co-morbidities (e.g. 'smokers with COPD) are not acceptable. See also outcomes regarding comments made by SEPAR (Smoking Prevention Group of the Spanish Respiratory Society) on this issue (line 234 and section 4.4).*
Section 4.5	4.5.2 – not relevant to look for drug interactions for NRT because users already taking nicotine during smoking – would be needed for NCE's. Line 259 - This should be clarified. The choice of post treatment assessment should be made with consideration of the PK profile of the product. Assessment immediately after discontinuation may reflect psychological effects of discontinuation whereas pharmacological effect might only be seen when the test drug has substantially cleared from the body (in the case of treatments with longer half lives this might be several days post discontinuation.) Line 262 – Where appropriate, compensatory smoking should be assessed. The guideline is silent on the combination use of NRT with other treatments for tobacco dependence and also on the possibility of an adjunctive therapy approach being taken – these should be included.	**Outcome:** *It is already stated in section 4.3.1.that ' For line extensions of established products like NRT, reference may be made to earlier studies'. This also apply for PK and PD interactions.* **Outcome**: *See answer above line 150* **Outcome:** *In principle, compensatory smoking should be evaluated for all new active compounds. It is not expected that this would be a large effort, as number of cigarettes will be anyway be registered in non-responders. Based on their pharmaceutical action, compensatory smoking might be specifically relevant for vaccines. Compensatory smoking is therefore also mentioned under 4.5.2 Specific adverse events, Nicotine-conjugate antigens* **Outcome:** *For the registration of a new drug, the proof of concept and benefit-risk balance of the new compound needs to be evaluated. Preferably, this is done for monotherapy, as the efficacy and safety profile of the drug alone could than be estimated without bias of co-treatments.*

		Add-on studies with e.g NRT can be submitted as supportive studies, and is considered as relevant information for treatment guidelines, but cannot be required from a regulatory point of view.

SUMMARY OF OUTCOME TO COMMENTS ON THE *DRAFT GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF SMOKING* (EMEA/CHMP/EWP/369963/05)

Introduction

In response to the draft Guideline, several comments were received from opinion makers of the smoking research field (such as the Society for Research on Nicotine and Tobacco (SRNT) and the Royal College of Physicians (RCP)) and representatives of industries (such as EFPIA, European Federation of Pharmaceutical Industries Associations, AESGP, Association of the European Self-Medication Industry and PAGB, The Proprietary Association of Great Britain), that the guidance may not rule out smoking reduction as a treatment option, and that the cut-down-to-quit approach should be included in the guideline. Several comments were made that nicotine dependence should be considered as a chronic disorder, needing chronic treatment. In addition, several experts expressed their fears that the proposed primary endpoint of one year continuous cessation without drug is a too high hurdle for new products, and would hamper product development. Finally, several experts suggested that studies in pregnant women should be required (amongst others the National Association of Women Pharmacists, UK).

As several comments that were made were of similar nature, some of the main issues that were raised are discussed in this section.

General comments

This guideline is meant to provide guidance for the development of new active agents in treatment of smoking, rather than development of new formulations of established products, such as NRT. This guideline is neither meant as treatment guidance.

Smoking reduction as primary outcome

Though we highly appreciated the input of experts and will certainly take several remarks into account, there is yet not sufficient evidence that smoking reduction would be a suitable endpoint for new products.

The main reason is that there is no strong evidence that smoking reduction would significantly reduce morbidity and mortality of smoking related diseases. E.g. long-term epidemiological cohort studies from Denmark showed that smoking reduction by 50% or more in moderate-severe smokers (>15g/day) did not significantly affect mortality rate due to tobacco related cancer, cardiovascular diseases and pulmonary diseases compared to continuous smokers (Godtfredsen, Am J Epidemiol. 2002;156(11):994-1001).). Neither had smoking reduction a significant effect on the incidence and time-to-event of the first hospital-admission for COPD and myocardial infarction in these studies (Godtfredsen et al, Thorax. 2002; 57(11): 967-72). Smoking reduction had however a small but significant effect on the risk on one specific form of tobacco related cancer, i.e. lung cancer (a reduction of 27% (2-46) compared to continuous smokers) (Godtfredsen et al, JAMA 2005; 294(12): 1505-10.). The risk on lung-cancer was however considerable more reduced in complete quitters (by 50% (31-66)) and in ex-smokers at baseline (by 83%) during 10-15 year follow-up. As far as we know, no other longitudinal studies are available where the effect of smoking reduction has been systematically investigated besides the quoted studies. These studies are however considered to be representative: they are reasonably large (N nearly 20,000), have a long-term follow-up of 10-31 years, there was limited loss-to-follow up, and the Danish data-bases allow that data from diagnostic disease and mortality databases can be coupled. Moreover, the Danish studies confirmed prior knowledge that smoking cessation indeed reduces significantly the mortality and morbidity risks, indicating power and validity of the studies. The findings of these epidemiological studies are supported by case-control and longitudinal studies. E.g., smoking reduction had no significant effect on FEV%, a relevant parameter for pulmonary functioning, though there was a small effect on cancer biomarkers by smoking reduction (Pisinger et al, Nicotine Tob Res. 2007; 9 (6): 631-46). The clinical relevance of a decline in cancer

biomarker values remains however unclear.

Why smoking reduction does not significantly contribute to health improvement whereas quitting does, may be due to compensatory inhalation (i.e. the limited number of cigarettes may be inhaled deeper or smoked more completely) or underreporting of the actual smoking level. In smoking reduction trials, biomarkers of smoking and carcinogenic biomarkers declined less than the reported number of cigarettes, which may be considered as a sign of compensatory inhalation (E.g. Wennike et al., Addiction 2003; 98(10): 1395-1402, Hatsukami et al., Cancer Epidemiol Biomarkers Prev 2006; 15(12): 2355–8). Another reason may be a high relapse rate to the former high level of smoking that is reported in harm reduction trials.

Although these studies show a diminished risk on lung cancer by smoking reduction, this does not mean that smoking reduction could be considered as an ultimate treatment goal, as myocardial infarction and COPD, which have a large public health effect, were not diminished by smoking reduction. Moreover, the effect of quitting on lung cancer incidence was considerably larger. Therefore, smoking reduction is not considered a suitable treatment goal, as the clinical benefit remains unclear.

Smoking reduction as an intermediate treatment goal

It has been postulated that smoking reduction might form a step towards complete cessation. Some experts advocate the 'cut-down to quit' approach as an alternative clinical treatment option for patients not able or willing to stop abruptly. It seems plausible that quitting from a lower level of nicotine use may be easier to access than from a high smoking level, as withdrawal symptoms may be less severe. From the International Tobacco Control Policy Evaluation 4-Country Survey (ITC-4) it became clear that many smokers decline their smoking frequency preamble a (unassisted) quit attempt (Cheong et al, Nicotine Tob Res 2007;9:801-10). According to the EMEA guidance document, the 'cut-down-to-quit' approach can be applied in trials (see Scope section). However, evidence should be provided that in the end complete and sustained abstinence is achieved, as the clinical benefit of reduction is not considered evident.
Smoking reduction is neither accepted as clinical endpoint, as, currently, evidence is lacking that smoking reduction indeed leads to sustained abstinence for a prolonged period. Smokers, who were able to stop abruptly (cold turkey), were more successful in quitting than gradual reducers according ICT-4 survey (Cheong et al, Nicotine Tob Res 2007;9:801-10). Up till now, only point-prevalence data of abstinence are reported in smoking reduction trials (for overview see Wang, Health Technol Assess. 2008 Feb;12(2):iii-iv, ix-xi, 1-135).

In conclusion, there is yet no sufficient evidence that smoking reduction would lead to a significant health benefit, and therefore smoking reduction is not a suitable endpoint for new products. The 'cut-down-to-quit' approach may be applied in the studies, though evidence should be provided that reduced smoking indeed leads to sustained cessation in the end.

Primary clinical endpoint: one-year of continuous abstinence.

The ultimate treatment goal is permanent abstinence. Products that only induce a short period of abstinence are not considered relevant, as health benefits are only achieved at prolonged abstinence. Relapse rates are known to be high in smoking. Short-term follow-up or on-treatment efficacy data are not sufficient as these data may not allow accurate prediction of long-term cessation, especially for new active agents. From epidemiological studies and randomised controlled trials it is known that the probability on relapse is the highest within the first year, and than gradually stabilize afterwards. Therefore, the required follow-up is one year.

Choosing the end-of-treatment as starting point for efficacy measurement may facilitate direct comparisons between different treatment durations or different drugs. However, it is acknowledged that cessation achieved during active treatment is also clinical relevant and should be taken into account, and that the one-year <u>off drug</u> period may not be feasible for long-term treatment options as expected for possible future long-term treatment options like vaccines. Therefore, the primary endpoint is adjusted, in a way that it should reflect continuous abstinence for a follow-up period of one year after randomisation. In the evaluation, the so-called grace period, where slips are allowed, do not need to be taken into account. For long-term treatment options exceeding 6 months of active treatment, the observational period should cover the follow-up period after end-of-treatment for at least 6 months, as relapse rates tend to increase sharply after stopping active treatment.

It is not believed that an endpoint including follow-up of 12 months after randomization would significantly hamper product development, especially now the 1-year off-drug follow-up requirement has been relaxed. In several studies with established products, such as NRT and varenicline, it has been demonstrated that continuous abstinence rates were superior over placebo after a period of one year, even after short term treatment (e.g. Etter & Stapleton, Tob Control 2006;15:280-5)). These results indicate that sustained abstinence till 12 months may indeed be a feasible and reasonable goal for new products.

Chronic treatment and relapse prevention

Several commentators stated that smoking and nicotine dependence should be considered as a chronic disorder, which should be treated chronically. According to this guideline, claims for relapse prevention can be made, but these should be justified by randomized parallel treatment withdrawal studies. Claims regarding recycling treatment in patients, who relapsed after initial success, should be substantiated by studies as well (see section 4.3.3).

Pregnancy

It is not supported that new agents will be tested in pregnant women, before broad post-marketing experience has been obtained. Several side-effects become only obvious once a large population has been exposed. Post-authorisation data of exposure in pregnant women should however be gathered and reported to the authorities (for guidance on this issue, see Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data EMEA/CHMP/313666/2005). Once a product has been registered, companies are encouraged to perform epidemiological studies on accidental use during pregnancy, but companies cannot be forced to perform trials in pregnant women.

It is beyond the scope of this guideline to make statement about benefit/risk balance of established products like NRT in pregnancy.