European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS FOR CARDIOVASCULAR DISEASE PREVENTION (EMEA/CHMP/EWP/311890/2007)

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	European Federation of Pharmaceutical Industries Associations (EFPIA)	BE
2	European Society of Cardiology (ESC)	
3	PSI	
4	Hofmann la Roche	
5	Wyeth Pharmaceuticals	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW

Summary of general comments and foci of comments:

Overall the comments are positive with regard to the development of a guideline for cardiovascular prevention. The approach to differentiate between integrated global risk scores models and CVD risk estimation based on cardiovascular disease is welcomed. In addition to several specific remarks there were some foci of comments.

- There were several comments on the level of the cardiovascular risk in asymptomatic patients with established risk factors as compared to risk in patients with established cardiovascular disease. The comments were taken into account and the first paragraph was revised accordingly.
- A major issue for discussion was the level of confidence and consistency required for subgroups. It was questioned that it should be stated that "study results in all sub-groups should be consistent". The statement "population in each subgroup should be large enough to support subgroup analysis with sufficient statistical power to draw reliable conclusions on the consistency of treatment effect" should not be interpreted as asking for statistical significant results in subgroups. The request for stratification for clinically relevant subgroups was also questioned.

  The term subgroups was specified by the term "relevant for prognosis". The sentences were kept in the document, however for the following reason. When choosing an integrated global risk score as the main inclusion criterion, there may be considerable inhomogeneity with respect to underlying risk factors. E.g. if an antihypertensive drug is tested in a risk based prevention study it is crucial that the results for both subgroups of patients with and without hypertension are reliable on their own. This does not necessarily imply that a p value of <5% is required in each of the subgroups, but estimates for the treatment effect should show consistency. Such consistency provides confidence that the overall finding also applies to relevant subgroups of the patient population. In the above mentioned example stratification for hypertension is recommended. On the other hand the document strongly recommends to avoid to include patient groups into the trial, where it can be assumed that the respective treatment effects in the (e.g. two) subgroups of the patient population would come up with significant heterogeneity. In a highly homogeneous population consistency of the results and lack of a trend (e.g. a p value from the heterogeneity test is greater than 0.15) may be sufficient.
- The requirement to optimize baseline therapy was questioned. This is of paramount importance, however. Showing cardiovascular prevention in patients not adequately treated may raise ethical concerns and may not be sufficient to demonstrate safety and efficacy.
- There were comments on the regional specificity of risk-scores, on the transferability and on the usefulness in global studies as compared to defined cardiovascular disease. Such comments were integrated.

General comments by organisations:

We welcome this draft guideline in this area and its repositioning as "cardiovascular disease prevention" instead of "secondary prevention" is appropriate. The draft guideline does not give detail about specific disease areas, but rather gives mostly generic considerations and recommendations for study design, which is appropriate.

A few major issues have been identified which are discussed further in this document and for which rewording is proposed in the below table:

- Two approaches of defining the target population at cardiovascular disease risk are discussed 1) integrated global risk score models and 2) CVD risk estimation

based on clinical symptoms. This provides flexibility, which is helpful, however CHMP also need to consider the global nature of studies;
- The draft guideline discourages mixing patients with significantly different absolute risk levels, however we consider this should be balanced with some flexibility depending on the circumstances;
- Of concern is also the assertion that "study results in all sub-groups should be consistent" which should be in our view revised
- Finally, regarding placebo controlled studies and the need to optimise the background therapy and life-style modifications, which are described as of paramount importance, we consider that flexibility is needed from the CHMP on this point as these may differ in different parts of the world, as clinical trials are in many cases conducted multi-nationally to support global development.

For statistical issues, it would be preferable to refer to the relevant statistical guideline where appropriate (see detailed comments below).

The guidelines have been added.

The document is reflective of current and up to date global thinking regarding the conducting of clinical trials for CV prevention.
Generally, the content is clear and not too ambiguous.
We are glad to read that primary/secondary prevention have been replaced by a more comprehensive strategy focused in high risk of CVD.
A clear and comprehensive definition of Multiple Risk pts/High risk pts should be proposed.
It would be helpful to get references of publications to support statement like in line 12, 58, 59.

We welcome the issuance of the above-mentioned draft guidance, and trust that the EMEA will take our two comments below into consideration.

SPECIFIC COMMENTS ON TEXT

1. INTRODUCTION

Line no. + paragraph no.	Comment and Rationale	Outcome
7-12	However, ~~with the discovery that patients with asymptomatic atherosclerotic disease or diabetes had a prognosis as grave as patients with established CVD,~~ **as** the terms primary/secondary prevention **do not truly represent inherent cardiovascular risk, they** have yielded their place for a more comprehensive strategy aimed at treating patients at high risk of CVD. These include patients with multiple risk factors and a 10-year risk of ~~coronary events > 20%.~~ **cardiovascular mortality > 10%.**	The examples of DM and asymptomatic atherosclerotic disease or DM as examples of a grave risk need some nuancing. Therefore, a more general statement is preferred. CV mortality has replaced risk for coronary event. *The text has been changed.*
8	All patients with diabetes do not have a prognosis as grave as CVD patients	Introduce "some" in between as and patients *Agree with the opinion. The sentence has been deleted.*
9-10	The terms of "primary prevention" associated with "at high-risk"are problematic since it can lead to undertreatment of those individuals. One should keep this concern in mind.	

Page 3, §1 Line 10	What is the scientific basis for the statement "patients at high risk of CVD include patients with multiple risk factors and a 10-year risk of coronary events>20%"? 1. Another cut-off could be envisaged 2. Some patients with a high (>20%) CVD risk may have only one risk factor. They are still worthwhile to treat and such a medication would still prevent CVD. A rewording is thus, proposed.	These includes patients with **<u>one or</u>** multiple risk factors and a 10-year risk of coronary events>20%. *The text has been adapted.*
10-12		Replace 10-12 by " ..adopting the intensity of preventive interventions in accordance with the total CV risk. Using the SCORE model, recommended for Europe by the 3rd and 4th Joint European Task forces of the guidelines on CVD prevention ,a score of >=5% of dying from CVD within a 10 year period is considered as high risk. This population thus represents the top stratum of CVD risk within the asymptomatic population and has a prognosis equivalent to some patients with documented CVD." *Agree. The text has been changed accordingly.*
9/10/11/12 14/15	Glad to see that the continuum of risk has replaced primary/secondary prevention in the thinking The 10 year risk of coronary events is based on the Framingham score which is known not to be extrapolable to every population over the world In general it would be helpful to get references of publications to support statement such as in line 12.	None A definition of the risk encountered by patients should be based on a consensus across continents (which score to use, gathering all known risk factors etc…) *The first paragraph has been changed.*
19	Global risk is the concept discussed at congresses for some time so this needs to be considered for trials, consequently this way of thinking is good	None
3. LEGAL BASIS		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**

Lines 25-42	Reference is made to the list of guidelines (lines 28-33). These guidelines refer to different indications, etc. We recognize that the associated guidelines listed in this section are provided for reference and should be read in conjunction with this guideline. However, it may be implied by some persons after reading this guideline that an outcomes trial demonstrating an outcomes benefit is needed for all of the clinical investigational study types listed on lines 28-33. The need for outcome studies will depend on the specific product and the nature of the claimed indication. For example, medicinal products developed for symptom relief (e.g., angina relief) may not be expected to have an outcomes benefit although it is understood that cardiovascular (CV) safety will need to be demonstrated.	Therefore, for clarity we suggest the addition of the following sentence immediately prior to line 41. "These guidelines are listed for reference; the need for a cardiovascular (CV) outcomes study is not applicable for all CV indications, but will depend on the specific product and the nature of the claimed indication." *Disagree. The aim of the document is cardiovascular prevention and not symptomatic treatment.*
4. CLINICAL TRIALS		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
62-64	These Framingham equations display risk of any ~~coronary heart disease~~ **cardiovascular** event, fatal or non-fatal based on categories of age, sex, smoking status, total cholesterol and systolic blood pressure.	The Framingham equations also make other CV risk assessment than coronary risk. *Accepted*
Section 4.1 Page 4, §2 Line 65	This is debatable that "*a 10-year absolute risk of 20%*" should be used as a threshold for intervention. A rewording is thus, proposed.	Using these scores a 10-year absolute risk of 20% has been recommended as a threshold for intervention**. However, this threshold is debatable and lower risk levels could be considered for initiating the treatment.** *The text has been adapted in a modified form according to the proposal.*
47	Preventive efforts most efficient when at high risk? Correct if this concerns the individual level but on a population level general measures to lower risk groups may be more effective	On the individual level, preventive efforts.....at highest risk. However on the population level, preventive efforts may be more effective if directed to the larger groups of individuals at moderated risk. *Agree. The text has been adapted accordingly.*
48	Prevention should be aimed where the need is greatest for any disease/illness	None
53	The former approach is only recommended in the asymptomatic apparently healthy population!	*Agree*

55-72	It is unclear if the term synergistic is appropriate in this case The concept of the SCORE system is good but having tried to use it in a clinical trial (ECLIPSE, Faegemann et al) it is not something well accepted by physicians. In designing clinical trials the concept of high risk needs to be easy to define. Framingham or a modified version seems easier to put into practise. SCORE does appear to have reasonable correlation with other indices although it is a mortality index However they make the reasonable statement that regional differences will be reviewed. In large trials it is important, especially global ones, that inclusion/exclusion is consistent. Using a less globally used method like SCORE is only really applicable to EU trials and even then not all physicians are familiar with it. Since this guideline seems to accept that the results will be viewed from a regional perspective so it is not clear if such SCORE charts are useful for defining large numbers of patients. Once the CHD risk equivalents are included in a large study along with CHD then this type of patient assessment is less useful and is more suited to shorter trials or placebo controlled trials where the aim is to find patients who don't for example qualify for a statin and therefore could get statin v placebo. This was the way it was used for the COMETS study In other previous trials knowing a patient with no CHD or CHD risk equivalents is on a statin suggests they are of sufficient risk. SCORE etc. are more useful in clinical practise for predicting risk and treatment need. Large studies need to be simple so need to use simple inclusion exclusion criteria – SCORE charts especially for people already on	Use of additive or cumulative is suggested instead *Agree. The text has been adapted accordingly.* For large global outcome studies clinical symptoms/underlying disease is a better way and more efficient way of selecting patients compared to risk scores. Risk scores do help screen for low risk patients (suitable for placebo vs. statin or even CETPi v placebo) and high risk primary prevention patients (also considered risk equivalents). *Agree. The points have been included in the text.*

	treatment are difficult to use. For lipids they only work for statin naïve data.	
58		Has a minor effect *Agree*
70		Since the chart predicts only fatal events, the threshold for high risk is defined as 5% or greater 10 year absolute risk. *Agree*
73-77	The SCORE group provided two risk charts: one for high risk regions in Europe, another for low-risk regions. Another important advantage of SCORE is that because it is limited to the prediction of fatal CV events, calibration at the national level is possible; this has already been done in different European countries. These calibrated national SCORE charts are the closest one can get to the real situation in a given community.	*Agree. The issue of regional differences and the differentiation of the SCORE system is reflected in the text.*
75-77	Regional differences in risk profile are expected, therefore, the Applicant will be requested to justify the relevance of the submitted data for the EU populations **taking into account that some integrated global risk scoring models (e.g. SCORE) have been adapted to countries with high and low cardiovascular risk.**	The SCORE has already been adapted for low and high risk countries. *Accepted*
Section 4.1 Page 4, §3 Line 76	The main objective in defining the target population is to accurately estimate the level of risk. Moreover in essence, the aim of the various scoring systems is to determine an absolute risk for some kind of events to occur without any interference with the underlying causes. Consequently it should not be required to justify regional differences in risk profile. A rewording is thus, proposed.	The Applicant ~~will~~ **could** be requested to justify the relevance of the submitted data for the EU populations. *Disagree. In a global study the issue of regional differences in CV risk has to be addressed in case a risk score is chosen as a main selection criterion.*

78	*-Risk estimation based ~~on clinical symptoms~~* ***on the presence of cardiovascular disease***	The last chapter focuses on both clinical symptoms and CV risk, including patient without symptoms. Thus, the title has been adapted. *Agree*
85-88	Good that risk equivalents e.g. diabetes are positioned that way	None
Section 4.1, Page 4, §4 Line 91	This should not be understood as an exhaustive list. Other clinical features such BMI or metabolic syndrome should be taken into consideration. A rewording is thus, proposed.	In addition to overt arterial disease criteria, several major atherothrombotic risk factors may be utilised for patient selection~~:~~ **e.g.** diabetes, diabetes nephropathy, low ankle brachial index, asymptomatic carotid stenosis > 70%. *The text has been adapted.*
92		For patient selection: eg diabetes, *Agree. The text has been adapted accordingly.*
94-100	Interesting point re mixing populations – ILLUMINATE did!	None
Section 4.1 Page 4, §5 Line 95	In some cases however results of studies may change the level of risk at which prevention is warranted. Moreover it may also be one of the objectives of the study to further investigate this threshold. Consequentially absolute threshold in some cases may not be always pre-specified. A rewording is thus, proposed.	The main objective in defining the target population is to accurately estimate the level of risk and to select high-risk patients or patients with a risk level at which a preventive therapy is indicated, **although in some cases pre-specified threshold may not be needed.** *The text has been adapted.*
95-96	The two approaches described above may be used to select patient populations for prevention trials, **both combined or separately**.	So far, no major trials have been submitted that included patients on the patients of CV risk per se. However, this may change and this should be mentioned. *Agree*
Section 4.1 Page 4, §5 Line 99 to 102	This is too a strong statement and in addition, flexibility should also be allowed, to include different risk levels, if appropriate A rewording is thus, proposed.	~~Mixing~~ **If** in the same trial, patients with significant different absolute risk levels **are included**, ~~is discouraged. If clinical subgroups of patients with similar level of absolute CVD risk are to be included,~~ the population in each subgroup should be large enough to support **some consistency trend across** subgroups ~~analysis with sufficient statistical power to draw reliable conclusions on the consistency of the treatment effect~~.

		Disagree. If the global risk score primarily defines the group of patients inclusion of patients with large differences in the CV risk in the study population constitutes a general question mark for the risk based approach. In addition, patients with high baseline risk my drive the overall result even in case a benefit in patients with low risk is only borderline or clinically not relevant.
100-101 in paragraph 4.1	The statement that the "*population in each subgroup should be large enough to support subgroup analysis with sufficient statistical power to draw reliable conclusions on the consistency of treatment effect*" could imply the need to show statistical significance in each subgroup. Such a requirement implies an excessive regulatory burden. E9, Section 5.7 considers the assessment of consistency or uniformity of treatment effects as exploratory.	Remove this statement and refer to the ICH E9 guideline which requires evaluation of consistency of treatment effects across subgroups in an exploratory fashion while acknowledging that in most cases the subgroups may not have enough patients to guarantee large improvements in each group. *Disagree. See general comment above. . A distinction should be made between subgroups and "relevant subgroups (i.e. that have been pre-specified and are also used to stratify the randomisation).*
101-107	Fully agree with sub-group thinking	None
105-106	The statement "*consistency of study results in all clinical subgroups should be established*" ignores the fact that because of chance efficacy will appear larger in some subgroups as opposed to others.	Omit this statement and refer to ICH E9 guideline as above. *Disagree. See general comment above. Quantitative differences in efficacy are still covered by the term "consistency". Only a complete lack of efficacy or adverse effects in specific subgroups are not covered. If there is indication, that a certain subgroup has no benefit (or: the benefit is restricted to one subgroup, only and therefore the benefit for the other subgroups is likely to be negative), such finding can not be ignored.*
108-123	Fully agree with duration – surprised they do not say longer from a safety perspective	None
112-113	Treatment should usually last at least 12 months, ~~but longer periods are often necessary~~ **and preferably longer, notable when the intended use is lifelong. When the latter is the case, duration up to five years is reasonable.**	Long term follow-up is considered crucial, therefore the text has been enforced on this aspect. *Agree*
Page 5 Line 113-114	The guidance indicates "In patients with ACS, 6 months data are usually sufficient for evaluation of acute treatment effects, however to assess the CVD prevention, one year data are needed". We understand these recommendations are given as possible	**For example,** ~~I~~n patients with ACS, 6 months data are usually sufficient for evaluation of acute treatment effects, however to assess the CVD prevention, one year data ~~are~~ may be needed. *The text has been adapted.*

	examples in this general draft guideline. As such, for clarification, a rewording is thus, proposed.	
115	The importance of lifestyle should be stressed more clearly here	Studies trying to establish if lifestyle issues have been adequately managed, on top of optimal drug treatment, have to be carried out. *Agree in general. The text has included reference to lifestyle changes.*
Page5, §2 Line 115 & 116	The draft guidance indicates, "Studies have to be carried out on top of optimal treatment. It is crucial to implement mechanisms to ensure optimal baseline therapy and to control cardiovascular risk factors over the whole study period". It is proposed to replace optimal but current medical practice.	Studies have to be carried out on top of ~~optimal~~ **current medical practice** treatment. It is crucial to implement mechanisms to ensure optimal baseline therapy and to control cardiovascular risk factors over the whole study period *Disagree. There may be cases where current medical practice is not according to treatment recommendations and not optimal. E.g. regional differences in availability of drugs and procedures may be relevant.*
Page5, §2 Line 117	Why requiring a "sufficiently long run-in period prior to randomization ". Indeed a well-designed retrospective assessment should be allowed. It is proposed to amend the sentence which could read as proposed.	Depending on the group of patients this requires an **appropriate** ~~a sufficiently long~~ run-in period prior to randomisation. *The text has been adapted.*
Page5, §2 Line 119	Regarding the risk factors listed, it may be controversial to look at risk factors that are "unrelated to the presumed mechanism of action of a drug". A rewording is thus, proposed.	The clinical relevance of a treatment effect will be difficult to be assessed if patients are not on optimal baseline therapy or ~~if~~ **with** risk factors, e.g. like smoking habits, ~~unrelated to the presumed mechanism of action of a drug~~ ~~are influenced differentially~~. *Disagree. The sentence aims on examples like the following one: If a drug promotes cessation of smoking this may lead to a false positive result for CV endpoints. This is not a direct preventive effect of the drug, however.*
Page5, §4 Line 123	The wording "stratification for the analysis…" is not adequate as stratification is for the design of the study not for the analysis. A rewording is thus, proposed.	~~Stratification for the~~ **Prespecified** analysis of relevant subgroups is recommended. *Disagree. See general comments above.*
Line 123 in para 4.2	The current draft states that 'Stratification for the analysis of relevant subgroups is recommended.' This recommendation is not appropriate in this guideline as you do not need to stratify in order to carry out reliable subgroup analysis. Trials of CV prevention will necessarily be large enough to ensure sufficiently balanced subgroups. So statistical comparisons of subgroups will not be	Remove the sentence recommending stratification. *Disagree. (see general comment above) The sentence has been slightly modified (stratification should be "considered". While it is true that in large studies stratification is usually not needed to guarantee for balance, pre-stratification provides a pre-specified break-point for*

	subject to bias or loss of power through lack of stratification. Stratification is an unnecessary complication that will add administrative problems without any benefit. The analysis of safety and efficacy in subgroups can be carried out satisfactorily without this design feature.	*consistency assessment at the time of licensing of the drug. If then e.g. results for males and females are consistent, this is of additional value because then reassurance has been provided, that the overall finding is likely to apply to these two subgroups, too.*
Page5, §4 Line 127 to 129	Sometimes the target population may be broader than the one investigated in the comparator original pivotal study and/or labelling (e.g. contraindications). Accordingly there is a risk to deprive populations who could benefit from the drug of a valuable therapy. Especially when taking into account that very often prevention indications have to rely on one single large-scale pivotal trial. A rewording is thus, proposed.	With an active comparator every reasonable effort has to be made to make the study population as similar as possible to the study population in the original pivotal efficacy study of the comparator **although it is acknowledged that in some cases this may not be possible.** *Disagree. See general comments above. The wording has been slightly changed as follows: "Stratification of relevant subgroups should be considered."*
Line 127-129 in para 4.3	The need to make the study population similar to the original population supporting the efficacy of the active comparator derives from the need of supporting assay sensitivity when there is a **non-inferiority** design. For a **superiority** design there should not be such a requirement as the demonstration of efficacy does not rely on the efficacy of the active comparator.	Remove requirement that study population for a superiority study vs. an active comparator needs to use same population as that supporting efficacy of the active compound.. *Agree. The text has been adapted accordingly.*
Line 129 to 131 in para 4.3	The current text states that: 'A superiority or non-inferiority design are acceptable. If a non-inferiority approach ……and the primary end-point used' This text fails to provide adequate clarifying remarks about the use of non-inferiority designs in CV prevention trials. A major problem for such a trial is maintaining its quality to ensure 'assay sensitivity'. These studies are usually very big. Outcome rates can be very small. A very small failure of compliance or of completeness of follow up of all outcomes can seriously affect the estimate of the treatment difference. Such trials are most reliable when compliance can be assured, such as may arise in the case of an acute hospital procedure (anti-coagulant during an operation), and when follow up is complete in every patient. But at the other extreme, if treatment is taken at home, and if the difference in outcome is represented by, say, 100 deaths in 10,000 patients, it is almost impossible to achieve sufficient reliability for a non-inferiority trial.	Add more text to reflect the concerns described here. In general it may be advisable to design the trial as a superiority trial using an increased significance level (see CHMP guideline on choice of non-inferiority margin section 5). *Disagree. There is no difference between definition of a non-inferiority margin and a relaxed alpha level in a superiority trial with respect to assay sensitivity. In both instances assay sensitivity has to be demonstrated and defined independently. The possibility to run a superiority trial with a relaxed alpha level in comparison to an established active comparator is mentioned according to the proposal. Reference to CPMP/EWP/2158/99 is included.*

Line 131 to 133 in para 4.3	The non-inferiority margin for a serious outcome is generally difficult to justify. The CHMP guideline on choice of non-inferiority margin discusses this issue in section 5 and the guideline should reflect this document.	Add reference to CHMP guideline on choice of non-inferiority margin section 5. *Agree. The text has been adapted accordingly.*
Line 139 in para 4.3	'A placebo-controlled trial aiming at superiority is adequate….' Surely, it is more than 'adequate'. It suffers from none of the non-inferiority design problems. It provides an absolute estimate of the treatment effect for comparison with earlier placebo controlled trials of other agents (if they exist). Surely the substantial question is whether it is ethical.	Express the value of a placebo controlled trial more clearly but stress the ethical issue. *Agree. The text has been adapted accordingly.*
139-141	Optimised background therapy is fully supported by us	Needs to be realistic and accept target goal will not be achieved for all risk and all patients *Agree. Achievement of baseline treatment goals will be assessed at the time of application for a MAH.*
Page 5 Line 140-141	The draft guidance indicates, "In this case, optimising background therapy and life-style modifications becomes of paramount importance." It is to be noticed that Guidelines for what is optimised background therapy and life-style modifications are different in different parts of the world. A rewording is thus, proposed.	In this case, optimising background therapy and life-style modifications **are important** ~~becomes of paramount importance~~. *Disagree (see above)*
142-167; 187-195	When addressing CVD mortality vs. total mortality as efficacy and/or safety endpoint it should be born in mind that, depending on the target study population, CVD death might weigh differently on total mortality, i.e., the heavier is the CVD death component on the Total mortality endpoint the more likely is an effect of the drug on total mortality as well. All M&M studies with statins (individually as well as in meta-analyses) have shown consistently that statins could significantly reduce total mortality only when CVD death accounted for at least 50% of the total mortality endpoint. In trials where CVD was less than 50% of total mortality a significant benefit (sometimes not even a trend for improvement) on total mortality could not be seen in spite of a significant reduction in CVD death risk.	None

Page 5, §1 Line 143 & 144	The draft guidance indicates that "the primary endpoint should be the one used when estimating the sample size" It is to be remembered that sometimes the study should be powered for a secondary endpoint, and this should be allowed. A rewording is thus, proposed.	**<u>In principle</u>,** the primary endpoint should be the one used when estimating the sample size, **<u>although sometimes studies may be powered as per secondary endpoints</u>.** *Agree, the term "in principle" is added to the text. It is not considered necessary to go into the details of exceptions, however.*
143-167	Endpoint – good to see they accept components with objective evidence. Also good they say there should be clinical justifications for other less objective endpoints. Agree with statement re confidence re all-cause mortality when CV mortality is the measure Agree that any composite driven by one component is not robust	none
151	Rephrasing this sentence this way makes it easier to understand.	Total mortality is preferred over cardiovascular mortality as a primary endpoint or as one component of the primary endpoint. *Agree. The text has been modified accordingly.*
151-158	- Our local advisory board members and also ourselves consider that cardiovascular mortality is preferred over total mortality as primary endpoint. The same for morbidity. Total mortality is highly interesting from a safety point of view (potential side effects), but it is less sensitive in terms of efficacy. It's better to be included as secondary endpoint. This would lead to demonstrate drug efficacy from CV mortality outcomes and safety from total mortality. Total mortality demands a higher number of patients than CV mortality and doesn't add any relevant efficacy value. In summary CV morbimortality is a better indicator for efficacy than total mortality. - The choice of primary composite endpoint has always been a challenge, may be a 'regulatory' consensus will help to adopt an homogeneous "composite endpoint' when talking about a similar field of investigation (ACS, chronic CHD, CHF, Hypertension etc…)	"Cardiovascular mortality is preferred over total mortality as primary endpoint as drugs with potential effects on cardiovascular physiology show their efficacy value in terms of CV mortality and not in terms of total mortality…" *Disagree. The primary endpoint should contain the most relevant clinical events. A benefit in cardiovascular mortality is not of clinical relevance at all in a case were it is not maintained on the level of all-cause mortality. Patients do not care for the reason in case they die. It may be debatable, whether in non-inferiority studies cardiovascular mortality is preferred.* Regulatory Advisory Committees should be the drivers of adopting new components of composite endpoints

	- Also same trend, convergence of Relative Risk reduction or consistency of results should be stressed again and again	
155-156	Composite outcomes, **<u>including fatal and non-fatal CVD events,</u>** in which multiple endpoints are combined, are frequently used as primary outcome measures in randomised trials to increase statistical efficiency.	
Line 155-167 Paragraph 2	The draft guideline implies that composite endpoints are not acceptable or preferred and that only mortality as a single endpoint is acceptable. However, it may not be practical or feasible to power CV outcomes trials on mortality as the sole primary endpoint -- one must consider the patient population and the planned indication. For example, statin therapy is indicated for primary prevention to decrease the risk of CV events in high risk subgroups on the basis of consistent benefit in decreasing the risk of vascular outcomes, such as major coronary events. However, over the course of a 4-5 year study, the absolute risk of mortality (total and cardiovascular) was low in the primary prevention population (patients with no past CV disease). A large meta analysis demonstrated a trend, but not a statistically significant mortality benefit. It was concluded that, "…statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality." (Thavendiranathan et al., Primary prevention of cardiovascular diseases with statin therapy. Arch Intern Med 2006;166:2307-2313)	Therefore, for clarity, we suggest that the final guideline should acknowledge that composite endpoints of hard events (e.g., nonfatal myocardial infarction, cerebrovascular accident), which are considered plausible on a scientific and medical basis may also be appropriate depending on the patient population, even if the benefit is derived primarily from only one of these events. These composites can aid in the assessment of the benefit/risk of all expected associated events. They should be well defined on the basis of objective data, should generally not include clinical decision outcomes, and should be discussed with regulatory authorities in advance. *A clear statement that composite endpoints may be acceptable in case they include hard clinical endpoints is added. General principles apply (e.g. consistency of effects, contribution of all components, clinical relevance of the components).*
157	Composite endpoints are frequently used wrongly and give often the impression of better outcome than proven. It is unfortunately primarily used to market drugs, not to further science.	However, such measures....of results. <u>Therefore the use of composite endpoints is in general not recommended.</u> *Agree with concerns raised on composite endpoints but disagree with the conclusion. As a matter of fact, composite endpoints can integrate clinically relevant cardiovascular events. Even in the absence of a demonstrated benefit on all-cause mortality on its own, benefit with respect to myocardial infarction and stroke is of major clinical importance as well. In fact the paragraph now even explicitly states that they may be acceptable, when including hard clinical events.*

169		Replace “generally” by “often” *Agree. The text has been modified accordingly.*
169-171	In order to limit the number of secondary endpoints, it is not always appropriate to include all components of the composite as secondary endpoints. It may be reasonable to include some as “tertiary” or “other” endpoints.	Replace with: “If a composite primary endpoint is used, its separate components should be presented separately as well. Components that are clinically meaningful and validated can also be included as secondary endpoints. Absence of harmful treatment effects for any of the components of the composite, regardless of whether they are included as secondary endpoints or not, is desirable to support a claim of efficacy on the composite.” *Disagree. A composite primary endpoint should only contain the clinically most relevant hard events. These should be analysed as secondary endpoints as they are relevant on their own. Further definition of tertiary or quaternary endpoints is not deemed meaningful.*
169-186	Fully agree with statements re secondary endpoints/surrogates	None
172-173	The statement that the only way to control Type I error is by means of a hierarchical organization is too restrictive.	Replace with: “Any secondary endpoint on which a claim is to be made should be included in a multiple comparisons procedure appropriately controlling Type I error (see CHMP Points to Consider on Multiplicity in Clinical Trials”. *Agree. The text has been adapted accordingly.*
173		Replace “end-point” by “endpoint” *Agree. The text has been modified accordingly.*
174-186	Imaging techniques should be considered not only in early phase I/II feasibility trials for decision but also phase III to support “line extension” claim.	*Agree. Line extension for a established therapy may be supported based on established biomarkers. The example is added in the text.*
Page 6, §2 Line 175	The draft guidance indicates that serum markers are suggested for “both identifying asymptomatic individuals at risk and as surrogate endpoints” but these are two different situations. A rewording is thus, proposed.	Beyond the traditional risk factors and clinical event endpoints, non-invasive imaging techniques and serum markers have been suggested for both identifying asymptomatic individuals at risk and **/ or** as surrogate endpoints for clinical trials. *Agree*
175	We would appreciate that this guideline is aligned with clinical	So, it could be completed this line including in brackets some examples

	practice as much as possible. In this sense we think that this is a good opportunity to HDL be recognised by written as a new clinical surrogated marker (as LDL is now).	just after "…serum markers.." . i.e. LDL, HDL….providing clinical articles in which this trend is stated. *Disagree. The exact role of HDL measurements in the regulatory context remains to be established. The text summarizes examples of markers of target-organ damage. HDL does not fit in this category.*
Page 6, §2 Line 181	The guidance draft indicates that "cardiovascular imaging and biomarkers may merit regulatory consideration in several situations including dose-selection, early phase I/II feasibility trials for decision" but this is in our view, too restrictive. A rewording is thus, proposed.	Cardiovascular imaging and biomarkers may merit regulatory consideration in several situations including **but not limited to** dose-selection, early phase I/II feasibility trials for decision. *Disagree with change of the wording. The term" including" implies that there may be additional situations.*
186	Rephrasing this sentence the proposed way makes it easier to understand.	May be limited to the particular drug mechanism, the disease stage, and to the subpopulations studied *Agree. The text has been modified accordingly.*

5. CLINICAL SAFETY EVALUATION

Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
188-195	Agree with opinion re safety and sub-groups	none