25 February 2016
EMA/754705/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases' (EMA/CHMP/50549/2015)

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

Stakeholder no.	Name of organisation or individual
1	Antonio Carlo Bossi, Treviglio Hospital
2	AstraZeneca
3	European Society of Cardiology
4	Regeneron Pharmaceuticals, Inc.
5	EFPIA

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1. General comments – overview

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3	Observational data sets are always less robust than randomised trials, yet the document does not distinguish these types of data when it refers to meta-analysis. The risk of confounding is substantially higher in the former. Should this not be made clear just for the avoidance of doubt?	It is already stated in section 4.2.1 that a meta-analysis (or pooled analysis) should include data from phase II/III studies. There is no mentioning of inclusion of observational data in meta-analyses/pooled analyses and inclusion of observational data such analyses should generally be avoided to decrease the risk of confounding/bias.
4	Regeneron welcomes the initiative by the Agency in releasing this reflection paper and clarifying the Agency's approach in assessing cardiovascular (CV) risk of medicinal products for the treatment of CV and metabolic diseases. The reflection paper raises a question regarding the necessity of establishing and/or how to establish a CV risk assessment when developing products for certain rare patient populations such as homozygous familial hypercholesterolemia, and familial chylomicronemia syndrome. Such populations are too small to adequately gather substantial CV data in Phase II/III to support the meta-analyses approach, while the conduct of a specific outcome study would be essentially impossible. Reliance on a change in a particular biomarker(s) that might be perceived as adverse could also be potentially misleading as to the possible benefit/risk of a new intervention in such smaller disease	It is acknowledged that it might not be feasible to conduct a meta-analysis of phase II/III data, let alone a dedicated CV outcome study, in orphan/rare cardiovascular or metabolic diseases. As an example, rare lipid disorders are now mentioned. A more "risk-based approach" to evaluate the CV safety profile, taking into account all relevant (pre-) clinical data and/or beneficial effects on surrogate endpoints, seems more appropriate in such specific cases and could be further discussed in a Scientific Advice setting. This has now been added to section 4.1.

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	populations. The reflection paper would benefit from a small section addressing these rarer conditions in which an overall assessment of CV risk is still important. Specifically the addition of some guidance related to orphan indications and how to best evaluate CV risk and interpret data from biomarker evaluations in these settings, would enhance the utility of the reflection paper.	
5	EFPIA welcomes the opportunity to comment on this reflection paper. It is noted that this is a general document covering cardiovascular risk assessment for drugs under development for cardiovascular and metabolic diseases. EFPIA is concerned about the paper as it is, which is reflected by the comments and wish for clarifications. EFPIA suggest that the thoughts described in this paper are further discussed with the industry. EFPIA agree to the principles about raising CV concerns if CV safety signals emerge during development and to emphasize the importance of further considerations including seeking advice with the agency to assess the need for CVOTs. 1) EFPIA suggests that the general nature is emphasised, as develop for treatment of cardiovascular disease with the intention of lowering the risk are different from product developed for treatment of metabolic diseases, such as diabetes even though these products may lower the cardiovascular risk	1. The distinction between products in different therapeutic areas is now more clearly addressed in the revised paper. Therapeutic area-specific aspects will still be addressed in respective guidelines (such as for diabetes mellitus). 2. The revised paper attempts to focus more on how to evaluate CV risk and less on for which products this will be a requirement ("for products for which a CV safety assessment is considered as necessary") (see revised sections 1, 2 and 4.1). More detailed guidance with respect to when such an assessment indeed is needed will be given in therapeutic area specific guidelines. The main emphasis during the evaluation of the cardiovascular safety profile will, however, be on clinical outcome data generated in a population that is representative for the intended target population (see section 4.2). Deviations from these general rules might

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	2) Medicines being developed with the purpose to reduce CV event is suggested to be discussed outside the scope of this paper. EFPIA also suggest leaving out disease specific details and refer these to specific therapeutic guidelines. E.g. in EMA's previous position on LDL cholesterol, LDL was as an accepted biomarker of cardiovascular risk, hence as novel LDL cholesterol lowering drug that has no theoretical cardiovascular safety concerns and no evidence of deleterious cardiovascular signals, these seems not to be in scope as they may need to demonstrate efficacy on CVD outcomes. (At a recent PCSK9 EMDAC meetings the FDA said that ruling out increased CV risk would not make sense for drugs to lower LDL). In addition, diabetes products which have benefits beyond reducing CV risk, have been discussed intensively during 2015 due to completion of several Cardiovascular Outcome Trials (CVOTs). Therefore the collected experience within the treatment of diabetes is therefore more detailed compared to other therapeutic areas; hence to make detailed statements covering all CV and metabolic treatments is not easy. 3) EFPIA suggest that the requirement to conduct cardiovascular safety assessments for drugs to treat diabetes be reconsidered. EFPIA question the general requirement to provide cardiovascular safety data to rule out a specific risk regarding new antidiabetic drugs. EFPIA agrees that long term follow up for safety is important for drugs that will be used chronically. In addition, EFPIA agree that the	be foreseen when the new drug is intended for the treatment of a rare disease (e.g. certain rare lipid disorders) or when there is already very strong evidence to exclude cardiovascular harm. The suggestion to remove all references to medicines that are developed with the purpose to reduce CV risks from the reflection paper is, however, not followed. An evaluation of the CV safety profile at the time of licensing is also considered relevant for these products and the current paper provides guidance and details on how such an analysis could be conducted. 3. There is no absolute requirement for a dedicated cardiovascular outcome study for all new drugs for treatment of type 2 diabetes in the current version of the paper. The need for conducting such a trial (either pre- or post-approval) should be based on the available data from the entire non-clinical and clinical development program, including clinical outcome data generated in a study population that is representative for the intended target population. Assessment of the CV safety profile is always an integral part of the overall benefit-risk assessment of new drugs for type 2 diabetes. 4. Cardiovascular safety issues can in some cases also be relevant for certain other cardiovascular drugs, e.g. in heart failure or angina pectoris, or for new drugs developed for non-cardiovascular diseases (i.e.

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	requirements for assessing the cardiovascular risk would be appropriate if there is a biologic, pre-clinical or clinical reason for cardiovascular concern. However without such a safety signal, EFPIA fails to understand the rationale for the cardiovascular safety assessment for drugs to treat diabetes. 4) The guidance appears to be driven by the fact that patients with diabetes are at increased risk of cardiovascular disease. However there are other conditions that increase the risk of cardiovascular disease such as rheumatoid arthritis or human immunodeficiency virus and a cardiovascular safety study is not indicated for drugs being developed in these areas 5) EFPIA suggest that agencies collaborate on best ways to investigate these kinds of safety aspects and potentially consider combined advices. Sponsors seeking CHMP advice is often combined with seeking advice from FDA. It is recognised that combined scientific advice can be part of this guidance but it would be an important step forward if FDA and CHMP/EMA could collaborate and provide mutual scientific advice. It would be hugely advantageous if FDA and CHMP/EMA would collaborate closely on how to handle documentation of rare safety events in clinical programmes including CV safety 6) EFPIA suggest considering potential conflicts between guidelines. This EMA/CHMP paper may conflict with the current FDA 2 step requirement to rule out cardiovascular	therapeutic areas not listed in section 3) if there are signs of an increased cardiovascular risk based on e.g. the mechanism of action and/or pre-clinical data. This has now been added to section 2. 5. Collaboration and exchange of information between EMA and FDA is already taking place for several disease areas and drugs, but can always be further expanded. For global drug development programs, applicants can indeed consider seeking a joint Scientific Advice from both EMA and FDA to discuss any specific issues relating to the assessment of the cardiovascular safety of medicinal products intended for long-term use in cardiovascular or metabolic diseases. 6. The 1.8 upper limit of the hazard ratio is regarded as a planning assumption and requires an adequate number of cardiovascular events in study/studies. This reflection paper allows for more flexibility than the FDA's *Guidance for Industry – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, also considering that the reflection paper covers a broader range of indications than just type 2 diabetes. Acceptability of data from meta-analyses and/or CVOTs presented at time of licensing will be based on its overall quality, the point estimates and confidence interval obtained for the calculation of the cardiovascular risk safety profile compared with the control group and the

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	risk with antidiabetic drugs. The FDA requests that an 80% increase in cardiovascular risk be ruled out at the time of filing and that subsequently a 30% increase in risk be eliminated as a post-approval requirement. However in order to maintain the integrity of the trial(s) in which the cardiovascular events are accruing to support the less than 30% increase in risk, the results from the first step (rule out 80% increase in risk) are to remain blinded to the company, the investigators and the public. Although the current EMA guidance suggests that the 80% increase in risk can be ruled out as part of trial or trials designed to rule out risk with greater precision, the requirement that the information be included in the filing, the European transparency regulations and the fact that the details are expected to be included in the SmPC will put the results in the public domain and potentially sacrifice the integrity of the ongoing outcome studies. EFPIA suggest that the CHMP/EMA clarify its recommendations, including the considerations of its discussions with the FDA, before a revision of the diabetes guideline regarding the possible impact of its own review and public disclosure of interim data on the “integrity” of a CVOT to be completed post-approval.	reliability of these estimations. If the use of interim data in a regulatory submission is considered, it is strongly recommended to discuss issues of trial integrity and validity of final study results with the EMA (see section 4.7). More specific guidance on these issues cannot be provided in the paper, as this will to a large degree depend on specifics of the development program of a new drug and/or the amount of clinical outcome data that is considered necessary to evaluate the cardiovascular safety profile of a new drug at the time of licensing.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
36-48	5	EFPIA suggest that the scope is described more clearly. It seems contradictive to combine products developed to reduce cardiovascular risk and products developed for treatment of metabolic diseases which effects might include a risk reduction, even though this is not the primary target of the drug development program. It is not clear if the rationale is only linked to a category of disease (e.g. “metabolic diseases”) or to therapeutic objectives related to CV outcomes (and approvals based on accepted surrogate measures). It need to be clear if conditions not cited but already covered in separate guidelines, such as heart failure or anti-arrhythmic indications or if these specific guidelines prevail. From this paper it is unclear what would be regarded as adequately characterization of CV risks. EFPIA suggest that the paper clarifies these very complicated assessments, including consider to distinguish between the treatments of cardiovascular diseases and treatment of metabolic diseases, and to refer details to the disease specific guidelines, which is expect to always prevail.	**Partly accepted.** See comments above for more details on the proposed changes in the revised version. As mentioned previously this paper intends to clarify the requirements for the evaluation of the cardiovascular safety profile at the time of licensing for new medicinal products intended for treatment of certain cardiovascular and metabolic diseases, which is now further specified in sections 1, 2 and 3 of the reflection paper .

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37-38	5	Comment: the reflection paper focuses on the development of medications for the “long term treatment of cardiovascular and metabolic diseases “(e.g. line 37 hypertension and hypercholesterolaemia) and metabolic diseases (e.g. type 2 diabetes and obesity)”. It is unclear if other CV and metabolic diseases than the ones listed as examples in lines 37 and 38 are in scope or not, e.g. depending on the therapeutic objectives, indefinite or limited duration of administration, etc. A wide scope would delay patient access to helpful medicines even where there is no reason to suspect an adverse cardiovascular effect. Proposed change (if any): *A revised paper should aim to clarify what conditions are in scope or not, and if the rationale is only linked to a category of disease (e.g. “metabolic diseases”) or to therapeutic objectives related to CV outcomes (and approvals based on accepted surrogate measures). This could be an opportunity to clarify whether the exclusion of 80% increase of CV risk based on a MACE endpoint may apply to conditions that are not cited but already covered in separate guidelines, such as heart failure or anti-arrhythmic indications (or if these specific guidelines prevail).*	**Partly accepted.** See previous comments for further details (this is now also further detailed in section 2 of the reflection paper).
69-71; 113-	5	Comment and proposed change:	**Accepted.** There is a general agreement that a product is

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120 Study population		In many situations it will be very difficult to demonstrate cardiovascular safety in a population that is representative for the intended population due to the low number of events in a low risk population. Presently CV outcome studies done for products developed for treatment of diabetes include mainly a high risk population (enriched) as the focus is to show no increase in CV risk. Hence it is recommended to adjust the wording line 70-71 and remove line 119-120. The following wording is suggested: *In either case, depending on the baseline cardiovascular risk, an adequate representation of high-risk patients (definition depending on the indication in question) should be enrolled into the study* EFPIA would recommend including guidance on the use of enrichment of trial population and to when and to what expend it is regarded as acceptable in the disease specific guidelines.	"safe" in a high risk population this can be extrapolated to a population with lower risk; ie, no principle objections to enrichment approach. The suggested change is implemented in section 4.3 and a caveat concerning the use of enriched populations is inserted.
70	5	Comment: EFPIA suggest that CHMP/EMA consider to include a shared focus between impact on MACE and impact on validated imaging modalities/functional assessment outcomes for CV risk	**Not accepted**. The main emphasis of the cardiovascular safety evaluation for drugs for which a more in depth evaluation of the cardiovascular safety profile is deemed necessary will be on "hard" clinical outcomes (MACE/MACE-plus). Validated imaging modalities/functional assessment outcomes for CV risk could be collected and presented as supportive data in the context of such a cardiovascular safety evaluation.

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75-96	5	Comment and propose change and questions: It is unclear what pre-specified means for a metaanalysis. This step would typically be done in the integrated summary of safety time frame, which would be after availability of phase III results. EFPIA suggest adding: *Rules and rationale for excluding a phase II or a phase III study should be presented* In general it would be helpful to clarify if statements in this section relate to guidance about the selection of data which contributes directly to the estimate of the treatment comparison, rather than about the selection of data which could be included in the analysis model (if an individual patient data metaanalysis is applied). For example, it would be helpful to clarify the intent of the following sentence: 'Information from doses below those proposed for marketing should generally be excluded from the meta-analysis'. Is the intent of this sentence that information from doses below those proposed for marketing should be excluded from the direct treatment comparison used to estimate the hazard ratio, rather than, that data collected on lower doses should be excluded from the analysis model? Data collected on lower doses, while not directly contributing to the treatment comparison of interest, could still contribute with valuable information to the model and allow for better precision.	**Not accepted.** Studies to be included in a meta-analysis should be pre-specified, in order to avoid a data-driven exclusion of studies. Important considerations on what studies and/or study data should be included or excluded in a meta-analysis are briefly discussed in the paper and reference is made to the CHMP guideline that specifically addresses the use of meta-analyses in applications (Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study (CPMP/EWP/2330/99)). **Not accepted.** Information from doses below those proposed for marketing should generally be excluded from the meta-analysis, since this could lead to an underestimation of the CV event rate. No change to current wording is considered necessary.

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		The following need to be more clearly described; For safety, should the metaanalysis also include all doses rather than the doses proposed for marketing? Is the guidance different for studies which focus on CV efficacy? How is higher and lower doses that the proposed marketing dose to be used in the assessment? The language around the trials to be included in the metaanalysis should be softened or a specific exception noted to allow the incorporation of a longer duration outcomes trial as part of a metaanalysis with other shorter trials in a development program. Please clarify what term "studies with negative outcomes".	**See previous comment**; information from doses below those proposed for marketing should generally be excluded from the meta-analysis. Information from higher doses than the proposed dose for marketing is considered more informative for an assessment of the CV safety profile and should generally be included and analysed in a meta-analysis. **Not accepted.** As already mentioned, trials with substantial differences in trial design (e.g. different treatment duration, or duration of placebo control) should not be included, unless it can be justified that they contribute equally to the question of interest. **Accepted.** The term "negative studies" refers to studies with a negative outcome for the primary endpoint (also called "failed studies"); this is now specified in section 4.2.1.
94	5	Comment: The possibilities for meaningful subgroup analyses may be limited due to the expected low number of events in these preapproval meta analyses. One needs to consider very carefully what to look into and what not to look into in order to avoid misleading findings – and certainly in data set like preapproval MACE analyses where the need to look into sparse data may lower the critical assessment of data quality and statistical	**Accepted.** The main emphasis will be on the evaluation of MACE/MACE-plus outcomes. Data in subgroups could be analysed and presented, but should generally be interpreted with caution.

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		robustness.	
98-102	3	Comment: Again, the title of this paragraph suggests only to look at CV risk (harm), but the reflection paper should also cover evaluation of the potential of a new product to reduce CV events (efficacy). See our general comments. It would be better to call this section: 4.1 Evaluation of Cardiovascular Outcome.	**Not accepted.** See previous comments.
98-102	5	Comment: Clarification is needed on whether this CVOT would have to be completed before approval or as a post-marketing requirement e.g. a statement like provided the overall benefit risk would be supportive or not of a post-approval study. The first in class situation might lead to a disadvantage for the sponsor in case of a pre-approval request compared to a 2nd in class product. The wording “when the drug is a first in class” would appear redundant and should be deleted or further clarity provided on when it might be necessary e.g. in case of no pre-clinical signal.	**Accepted.** There is no absolute requirement for a dedicated cardiovascular outcome study for new drugs in the current version of the paper (nor was there such an absolute requirement in the previous version). The need for conducting such a CVOT (either pre- or post-approval) should be based on the available data from the entire non-clinical and clinical development program, including clinical outcome data generated in a population that is representative for the intended target population. As mentioned previously, reference to “first in class” drugs is now deleted in section 4.2.2.
97-112	5	Comment: There are limited comments in the paper on the use of interim data in a regulatory submission. In addition to the scientific advice and if a CVOT is required due to safety concerns, a way forward could be to include the CVOT in the RMP, and refer the outcome until completion, i.e. CVOT data should not be required to be available at the time of marketing	If the use of interim data from clinical studies (e.g. a CVOT) is considered in a marketing authorisation application, it is strongly recommended to discuss issues of impact on trial conduct, trial data integrity and validity of final study results with EMA. More specific guidance on these issues cannot be provided in the paper, as this will to a large degree depend on specifics of the development program of a new drug and/or the amount of clinical outcome data that is considered

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		authorisation provided the overall risk/benefit would be supportive. According to the transparency rule, is the clinical summaries and overview expected to be public available. Analysis of safety data is also expected to be released to the public, and even if these documents are redacted in files to protect the validity of ongoing trials, it is also required that the sponsor do not have access to interim analysis of blinded data, so to protect the integrity of CVOT it is proposed to provide the results of the CVOT until after marketing authorisation, and include these to be followed up upon in the RMP. The DMC will ensure the any upcoming safety signals will be addressed, if needed. <u>Duration of studies and size of safety database:</u> Guidance to support the design of CVOT studies including duration, exposure and the selection of a non-inferiority margin is suggested to be addressed in the disease specific therapeutic guidelines.	necessary to evaluate the cardiovascular safety profile of a new drug at the time of licensing. Concerning the second comment on guidance on duration of studies and size of safety database, an attempt is made to describe this in the reflection paper. It should, however, be noted that deviations from the general rules outlined in this reflection paper can be foreseen; if relevant, applicants are advised to seek Scientific Advice from EMA to discuss the data that are considered necessary for the evaluation of the cardiovascular safety profile at the time of licensing of a specific new drug.
102	3	Comment: In this way, second or third in class agents are favourite. Sometimes there are differences within the same class. Proposed change (if any): ~~or when the drug is a "first in class"~~	**Accepted.**

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102	5	Comment: The sentence implies a requirement *by default* for a dedicated CV outcome trial "when the drug is a first in class", as for products with an intrinsic risk due to MoA or observed safety signals. Although the importance of developing knowledge on innovative products, such as with intensive market monitoring, is acknowledged, imposing by default this burden in the form of a (pre-marketing?) CV outcome trial irrespective of specific MoA-based or observed safety concern seems excessive and would not promote innovation. In addition, the focus on "a first" in class somewhat implies a significant advantage (less requirements) for a follower product, irrespective of the general experience available on the class. EFPIA does therefore not consider this criterion valid to establish different regulatory requirements and would be a clear disincentive to innovation. Proposed change (if any): delete "or when the drug is a "first in class"", and keep a specific risk intrinsic to the MoA or an observed CV signal. A prospective, pre-specified meta-analytical plan should be a first option in the absence of specific concerns, in the context of the clinical benefit of the product and current Risk Management Plan strategies.	**Accepted.** A requirement of a CVOT by default for all "first in class" drugs was never the intention. Still, this sentence has been amended and reference to "first in class" drug has been deleted for further clarity.
104	5	Comment: A clarification that established products considered as	**Not accepted.** The current wording already states that: "A dedicated cardiovascular outcome study should have an

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		standard of care could be used as a comparator; and not require a thorough CV risk characterization of the product would be appreciated.	adequate control arm, and if an active control is used this should preferably be one for which the cardiovascular risk, or absence thereof, is already well characterized." No change to current wording is therefore considered necessary.
105-107	2	Comment: We would like the potential guideline to be more specific around the possible use of interim data from a regulatory perspective which is challenging, risks creating bias and ideally needs to be considered from a global perspective.	**Not accepted.** If the use of interim data from clinical studies (e.g. a CVOT) is considered in a marketing authorisation application, it is strongly recommended to discuss issues of impact on trial conduct, trial data integrity and validity of final study results with EMA. More specific guidance on these issues cannot be provided in the paper, as this will to a large degree depend on specifics of the development program of a new drug and/or the amount of clinical outcome data that is considered necessary to evaluate the cardiovascular safety profile of a new drug at the time of licensing.
106-109	3	Comment: Interim data should not be publicly reported to maintain the integrity of the ongoing trial.	**See previous comment** on use of data from interim analyses.
106-109	5	Comment: The recommendation to prospectively discuss planned interim analyses to support an application and to protect the trial integrity and validity of final results is understood. In addition, reference is made to the FDA August 2014 Public Hearing on non-disclosure of interim CVOT results, including by the Health	**See previous comments** on use of data from interim analyses. For global drug development programs, applicants can consider seeking a joint Scientific Advice from both EMA and FDA to further address these important issues in a timely manner.

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		Authorities (pre and post approval until completion of the study). Divergent approaches between the CHMP/EMA and the FDA in this respect would have important consequences in both regions, and could jeopardize such options irrespective of a prior Scientific Advice. Proposed change (if any): EFPIA suggest that the CHMP/EMA clarify its recommendation regarding the possible impact of its own review and public disclosure of interim data on the "integrity" of a CVOT to be completed post-approval.	
113-120	5	Comment: While the sentiment expressed here is nice in theory, in practice it will be difficult to ever balance the proportion of "high risk" and "low risk" subjects enrolled so as to guarantee similarly powered assessments of the hazard ratios in the two strata at the same points in time (e.g. interim and final) while also maintaining a similar degree of study duration. Indeed, to do so with any precision would generally require knowing the answer to the study question in advance. Proposed change (if any): Consider striking the last sentence (Line 119 – 120) ~~Ideally, an assessment of the cardiovascular risk~~	**Partly accepted.** If feasible, a comparison between "high" and "low" risk subjects could be considered useful when evaluating the CV safety profile of a new drug. It is, however, acknowledged that the robustness of such a sensitivity analysis depends on the number of events and subjects in each group and generally will require cautious interpretation. When assessing results from such studies, the main emphasis will always be on the total study population. The current version of the paper attempts to provide general guidance on the population of clinical studies that can be used to assess the cardiovascular safety profile at time of licensing of a new drug.

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		~~should be possible in both "high" and "low" risk patients.~~ Instead, concentrate on providing guidance to sponsors on how to best define the specific study population upon which the assessment is to be made (e.g. when is a high risk population preferred – leading generally to smaller and/or shorter duration studies vs. when is a low risk population preferred – leading generally to larger and/or longer duration studies).	
124-126	5	Comment: the duration of the follow up in pivotal clinical trials needs a clarification, specifically for compounds which MoA and available data do not suggest a CV risk. Can the previous guidelines be followed in this regard – e.g. recommended study duration at least one year for weight control drugs? The sample size would need to be adjusted for the appropriate quantification of CV risk. Proposed change: additional clarification for the section 4.4.	**Not accepted.** For drugs for which a more in depth evaluation of the cardiovascular safety profile is deemed necessary, the duration and follow-up periods of the clinical studies (both those included in a meta-analysis or a dedicated cardiovascular outcome study) should be sufficient to capture an adequate number of cardiovascular outcome events that might be caused by the study drug. More specific guidance on the exact duration of such studies cannot be provided in the paper.
124-126	5	Proposed change (if any): The sentence "Duration and follow-up periods of the clinical studies (both those included in a metaanalysis or a dedicated cardiovascular outcome study) should be sufficient to capture an adequate number of cardiovascular outcome events that might be caused	**Not accepted.** Suggested change unclear.

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		by the study drug." should be rephrased to something like "…..adequate number of CV outcome events necessary.	
124-126	5	Comment and Proposed change: The reflection paper states that the trial duration "should be sufficient to capture an adequate number of cardiovascular outcome events that might be caused by the study drug". Thus, it is only in the case of an excess risk it is possible to estimate and regard the trial duration as adequate. If no biological mechanism is known and no excess risk was reviled you won't know whether trial duration was too short. Hence, it should be clarified for products with known MOA and available data which do not suggest a CV risk, what would be regarded as appropriate study duration for pivotal trials e.g. would previous recommendation on study duration for at least one year for weight control drugs be acceptable? Realistically the probability of gaining an accurate assessment of CV risk in a development program is low and outcome studies will then be required. This section gives some optimism that the development program will be enough when that is unlikely to be the case (depending on the disease). Proposed change (if any): Duration of exposure should	**Not accepted.** See previous response to similar comment. For drugs for which a more in depth evaluation of the cardiovascular safety profile is deemed necessary, the duration and follow-up periods of the clinical studies (both those included in a meta-analysis or a dedicated cardiovascular outcome study) should be sufficient to capture an adequate number of cardiovascular outcome events that might be caused by the study drug. More specific guidance on the exact duration of such studies cannot be provided in the paper.

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		be consistent with the requirements in the disease specific scientific guideline e.g. the diabetes guideline, unless biological mechanism suggests that excess risk will only materialise later than 12 months. Appropriate measures should be in place to ensure follow-up until end of trial (not only end of treatment). In case of an excess risk a dedicated cardiovascular outcome study need to be able to capture adequate number of CV outcomes event necessary for the assessment of the products CV risk. In addition remove line 126-131	
130-131	2	Comment: Is there any standard that could be specified, ITT population for instance or is there any other, not pre-specified population that should be considered?	**Accepted.** The most relevant population may differ depending on the target population and product. The choice of population should be defined and justified a priori.
139-148	2	Comment: MACE and MACE+ are specified and exemplified – we would like to suggest that there can also be *alternatives* to or variants of MACE for particular conditions. Proposed change (if any): After line 141, enter a new sentence reading as follows: Alternatives to MACE may be considered for particular conditions if specified and justified.	**Not accepted.** The MACE-composite endpoint is the most widely used endpoint for an assessment of the cardiovascular safety profile of new drugs, since these components are considered the most clinically relevant and robust. Furthermore, use of this endpoint will enable cross-study comparisons of the cardiovascular safety profile of different drugs. The MACE-composite endpoint is therefore stated as the preferred endpoint in the reflection paper for both the meta-analyses and dedicated cardiovascular outcome studies in the paper. Inclusion of other components (i.e. in a MACE-

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			plus composite endpoint) can be considered on a case-by-case basis depending on the characteristics of the medicinal product in question. The use of a "MACE-plus" endpoint should, however, be properly justified a priori.
141	5	Comment: Suggested change in wording of current text: "stroke" Proposed change (if any): change stroke to "*non-fatal stroke"*	**Accepted.** Fatal strokes already captured in the "CV-death" endpoint.
142-145	5	Comment and proposed change: Hospital admission for heart failure as a pre-specified component of a composite cardiovascular outcome could be relevant in patients with metabolic disease, as a common and prognostically important cardiovascular complication of these conditions. Moreover, it is the one cardiovascular outcome for which the risk has been shown to be increased by some glucose-lowering therapies. Additionally a comma is missing from the text (see in red) Proposed change (if any): *"In some instances, depending on the characteristics of the medicinal product in question, additional cardiovascular outcomes like hospitalization for cardiovascular causes (e.g. unstable angina, need for*	**Accepted.**

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		*revascularization, acute heart failure or worsening of existent heart failure***,** Transient ischaemic attack (*TIA), and sudden death could also be included in a composite endpoint ("MACE-plus")"*	
147-148	2	Comment: With this definition we suggest that on page 6 line 147-148 it is clarified that analysis of individual components should include also fatal events, i.e. "fatal and non-fatal MI" and "fatal and non-fatal Stroke". Proposed change: Add to the sentence (in ***Italics***) 'The components of the selected composite endpoint should always be presented separately as supportive analysis ***and include also fatal and non-fatal MI and fatal and non-fatal stroke.***'	**Accepted, but no change considered necessary.** Fatal CV-events like stroke and AMI will be captured in the "CV-death" endpoint.
149-150	2	Comment: Clinical events of interest should be well and objectively defined in the protocol, whether or not adjudication is done. Adjudication will decrease variability in reporting and may make it possible to limit sample size. Depending on the type of patients and treating physicians, adjudication may however not always be needed and it may be more relevant to ensure that a large enough sample size is achieved. Examples of endpoints suited for this approach are all-cause death and all cause stroke as well as myocardial infarction which may be un-adjudicated if the treating physicians are trained and practicing cardiologists. Proposed change:	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In the first sentence, add the word '***pre-defined***' in the middle of the sentence: It is important to ensure that an independent committee adjudicates all ***pre-defined*** major cardiovascular event included in the composite endpoint.'	
149-150	5	Proposed change (if any): *"It is important to ensure that an independent committee adjudicates all major cardiovascular events included in the composite endpoint"*	**No change suggested in this comment.** This sentence (section 4.5) has, however, now been revised based on the previous comment from stakeholder #2: "It is important to ensure that an independent committee adjudicates all major pre-defined cardiovascular events included in the composite endpoint."
154-155	5	Comment: The description of additional parameters collected needs to be more precise. The list includes parameters which are not routinely collected in CVOTs. Parameters which may have limited relevance and which will require substantial efforts to systematically collect e.g. arrhythmias, cardiac imaging. Proposed change (if any): "*Additional parameters should be considered for systematic collection whenever a risk is intrinsic (based on the mode of action), or when safety signals have been observed in the pre-clinical studies, makes this relevant."*	**Accepted.**
155	1	Comments: Furthermore, a complete evaluation of potential drug-	**Not accepted.** Evaluation of drug-drug interactions is outside the scope of this reflection paper; this issue addressed in

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		to-drug interaction should be considered, both during clinical studies, both in the "real-world" setting. For this purpose, safety-data monitoring and reporting should be supported. Proposed change (if any):	other relevant CHMP guidelines.
157-159	2	Comment: We suggest that it is clarified if the recommendation is to design the trials to have sufficient statistical power to obtain an upper limit of the confidence interval (95%, two sided) for the Hazard Ratio (HR) below 1.8 under the assumption of a true HR≈1.	**Comment:** This is correct and stated in section 4.6. Other targets for the upper confidence limit (UCL), including narrower targets, may be more appropriate based on the particular target population, known cardiovascular risk profiles of the comparators, previous experience in the class, presence or absence of a signal for increased risk elsewhere in the dossier.
157-159	5	Comment and proposed change: As a general rule, assuming a comparison against a placebo or standard of care (SOC), the evidence based on cardiovascular risk should be planned to obtain an upper limit of the confidence interval (95%, two sided) for the Hazard Ratio (HR) below 1.8 in the event that HR≈1″. Proposed change (if any): *It should be stated clearly that this is the requirement for the entire study population. Important subgroups can be examined for consistency of effect, but the upper confidence limit (UCL) of 1.8 is not required for subgroups. In addition the guidance is needed on how*	**Accepted.** See comments above and section 4.6 of the concept paper. The cardiovascular safety profile should be assessed in the entire study population.

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		high the observed point estimate, HR, can be (with CI upper limit still <1.8) and still be accepted as ~1	
159	3	Comment: For anti-hyperglycemia agents the FDA has used an upper limit of 1.3 for the composite CV outcome. So EMA should justify this 1.8 upper limit. Proposed change (if any): Hazard Ratio (HR) below 1.3	**Justification:** The 1.8 upper limit of the hazard ratio is regarded as a planning assumption and requires an adequate number of cardiovascular events in study/studies. This reflection paper allows for more flexibility than the FDA's *Guidance for Industry – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, also considering that the reflection paper covers a broader range of indications than just type 2 diabetes. Acceptability of data from meta-analyses and/or CVOTs presented at time of licensing will be based on its overall quality, the point estimates and confidence interval obtained for the calculation of the cardiovascular risk safety profile compared with the control group and the reliability of these estimations.