2016-09-14

Submission of comments on 'Evaluation of anti-cancer medicinal products in man' (EMA/CHMP/205/95Rev.5)

Comments from:

Name of organisation or individual
International Society for Clinical Biostatistics: Statistics in Regulatory Affairs Subcommittee

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	General comment 1 – Adverse Events: We strongly support the revision of the "Guideline on the evaluation of anticancer medicinal products in man" with respect to improving the reporting of AEs. The guideline can be further improved by adding clear-cut recommendations for valid statistical analyses of adverse events based upon adequate survival time methods to perform an appropriate benefit-risk assessment. **General comment 2:** The guideline has been updated to the current development of anticancer drugs, which has evolved from cytotoxic agents to monoclonal antibodies and molecule-specific preclinical models to assess and predict anticipated activity, as well as safety. As the development processes have changed, it is necessary that the requirements for clinical trials are updated. Therefore, we welcome the new approaches of the guideline. **General comment 3- Section 5. Biomarkers:** The guideline encourages for the use of biomarkers for patient stratification. This is much welcomed from the ethical point of view. It enables the conduct of studies on the desired patients rather than exposing patients not in the target group, which will reduce possible unnecessary suffering. It also has the potential to shorten study timelines and thus possibly makes a new effective treatment available within shorter time limits. **General comment 4:** Quite often, benefit-risk analyses are only conducted at a group-level. However, it is of importance to consider both efficacy and safety together on the same patients. We suggest this is clarified in the guideline.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	General comment 5 – Abbreviations and Definitions: A number of abbreviations are used. Most of the time, an abbreviation is introduced it is clearly spelled out. However, sometimes the abbreviation is used without preceding specification (e.g. "ORR" in Section 2 and "SmPC" in section 4). **General comment 6 - Informative censoring (Appendix 1, page 3):** Instead of "There is no satisfactory way to correct for informative censoring…", the guideline should recommend sensitivity analysis which assesses sensitivity of the results to particular assumptions about informative censoring. This is entirely analogous to the situation of missing outcome data where the guideline rightly says "sensitivity analyses should be undertaken using different approaches". Convenient methods for sensitivity analysis to informative censoring are now available (see Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. *Stat Med*. 2014;33(27):4681-4694. doi:10.1002/sim.6274). **General comment 7 – Cross-over** 1. Discussion of cross-over is limited to the undesirability of allowing cross-over (lines 838-840 in section 7.1.3 on page 22 and Appendix 1 page 8). It is surprising that no mention was made of the ethical reasons for allowing cross-over, even though these ethical reasons can be overplayed. 2. Cross-over commonly occurs, and sponsors commonly attempt to "adjust" for it. Some guidance would be useful for this situation: in particular, the following principles are useful: a. if adjustment for treatment cross-over is planned, the methods to be used should be pre-specified and carefully justified in terms of the assumptions involved	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	b. data collection should be modified in the light of any intended adjustment methods, possibly involving efforts to collect complete follow-up data after cross-over, and/or collecting data on time-dependent prognostic variables which predict cross-over 3. To avoid possible confusion with cross-over trials, a term such as "switch-over" or "switching" should be used instead of "cross-over". **General comment 8:** Increasingly, anticancer products are developed on an accelerated basis with a Phase II or II/III designed for accelerated or full approval on the basis of a Phase I or Phase Ib expansion cohort. Although this represents something of an exception to the traditional development path, it is increasingly becoming an alternative norm. Under accelerated development, significantly less information about the product's safety and efficacy is known than in a traditional Phase III, and study designs rely heavily on assumptions and targets rather than data. We recommend a guidance section covering this path, including considerations on undertaking it and guidance on EMA's view of procedures, assumptions, and risks. **General comment 9:** Suggest addressing antibody-drug conjugates, which have properties both of cytotoxic compounds and antibodies. **General comment 10:** Suggest addressing delayed effects, e.g. of immunotherapies.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	General comment 11 - Safety: a. In some indications and investigational products, investigators may lack sufficient expertise to identify causality accurately. The sponsor may be better equipped to assess causality, but especially in blinded trials, involving the sponsor's experts may jeopardize the blind. Recommend discussing this issue and approaches to address it, e.g. unblinded experts not connected with the trial. b. Methods for evaluating safety per unit time or per exposure may involve strong assumptions, such as constant safety event hazards over time. Suggest mentioning these assumptions, and discussion of evaluating these assumptions, both in advance based on knowledge of disease and treatment mechanisms, and based on study data. **General comment 12 – Benefit-risk assessment:** Suggest citing the EMEA/CHMP/15404/2007 Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
90-91		**Comment:** The interpretation of PFS as relevant measure of patient benefit requires a patient-relevant definition of progression. **Proposed change (if any):** Add required criteria to interpret PFS as patient-relevant endpoint.	
95		**Comment:** A better term instead of "cross-over" is given by "treatment switching" because it cannot be confused with cross-over studies. **Proposed change (if any):** Replace "cross-over" by "treatment switching" or add an explanation so that confusion with cross-over studies is avoided.	
117		**Comment:** "… planned Appendix 2 will …": Appendix 2 is already available. **Proposed change (if any):** Delete the word "planned".	
121-132		**Comment :** Chapter I: Introduction (background) This section currently focuses more on revision history rather than being an introduction to the guideline. It is suggested to move this text to the end of the document and change the chapter heading to revision history. **Proposed change (if any):** Reconsider chapter name	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
121-132		**Comment:** It seems that the description of the changes is incomplete. Explanatory notes regarding the planned Appendix 3 are missing as well as comments regarding the main aim of the revision. (The aim of this revision was "to find ways on how to report AEs in order to improve the understanding of the toxicity and tolerability profiles of medicinal products.") **Proposed change (if any):** Add explanatory notes regarding the planned Appendix 3 as well as comments regarding the main aim of the revision.	
147-152		**Comment:** Chapter 2. Scope While we agree with this statement, it does not seem to fit under this heading and the purpose is not clear. If needed, it could be mentioned in the introduction. **Proposed change (if any):** Reconsider moving the text to Introduction	
210		**Comment:** Chapter 4: Pharmacokinetics A number of factors are mentioned for investigation of covariates (line 210). It should be added that all factors used as covariates should be medically justified. Just using factors as covariates without the knowledge whether these factors are of importance for disease progression may negatively influence the statistical power. **Proposed change (if any):** It should be added that all factors used as covariates should be medically justified.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
226-263 and 743-789		**Comment:** Section 5, Biomarkers, and also in Section 7.1.1, Patient population (for Phase III studies), appear to have some inconsistent statements. a. Section 5 Biomarkers, appears to require the sponsor to confirm specificity, i.e. that the treatment does not work in the biomarker-negative population to make a biomarker-based claim, with "convincing" evidence. *For patient stratification, if convincing evidence of biomarker selectivity is established early in the non-clinical and clinical development phase, confirmatory evidence in the negative population may not be required and such studies may be carried out in patients expressing the biomarker of interest.* (p. 7 lines 241-244) b. But section 7.1.1 appears to indicate a much lesser evidentiary requirement as a sponsor obligation; the sponsor can pursue a restricted label based on merely exploratory evidence unless a non-relationship is proved: *If exploratory studies provide a basis for including/excluding certain patients based on tumour phenotype/genotype, this will be reflected in the labelling. As a corollary, if patients with tumours not expressing the target for activity are eligible, a restricted labelling may still be appropriate if it has not been demonstrated, e.g. by subgroup analyses, that target expression is irrelevant for anti-tumour activity.* Suggest reconciling the two. In particular, suggest clarification permitting a sponsor to pursue a restricted label based on mechanism of action and pre-clinical data, without requiring definitive proof of specificity or evaluation in a full biomarker-negative population to ensure specificity. Where preliminary evidence of non-efficacy exists, enrolling biomarker-negative patients for the purposes of proving non-efficacy may be unethical and practically difficult, especially in the case of a discrete biomarker. In the case of a continuous biomarker, the cut-off may be somewhat arbitrary and imprecise with outcomes on either side of the cut-off similar, yet the treatment may be highly efficacious. Too high an evidentiary burden for specificity may be unnecessarily onerous and impede development of useful treatments.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
254-255		**Comment:** The setting of biomarker target performance is not mentioned in the Biomarkers part (Section 5). This is the subject of a recent paper entitled "Early-Phase Studies of Biomarkers: What Target Sensitivity and Specificity Values Might Confer Clinical Utility?" by Pepe M.S. et al., Clinical Chemistry 62:5, 737-742 (2016). **Proposed change (if any):** Lines 254-255 could read "...considered early in clinical development by setting a biomarker target performance and maximising the clinical..."	
284-330 and 406-472		**Comment:** Section 6.1.1 and Section 6.2.1. It would be desirable if these sections on "Phase I, single agent dose and schedule finding studies" with cytotoxic and non-cytotoxic compounds could include a subheading on or give a comment on "study designs for phase I studies" (similarly to sections on phase II and phase III studies). This would give more advice on how to best meet study objectives, such as identifying MTD, DLT, phase II dose, while at the same time minimizing risks for the patients. **Proposed change (if any):** Add further information on Phase I trials	
304-206		**Comment:** 'cancer patients without established therapeutic alternatives' It is important to define: a) 'cancer patients' using for example diagnosis criteria, and b) 'established therapeutic alternatives' (these alternatives may exist in one country but not necessarily in the country where the study will be conducted?) **Proposed change (if any):** -	
314		**Comment:** 'minimal toxicity' needs to be clearly defined **Proposed change (if any): -**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
350-358		**Comment:** Section 6.1.2: Selection and number of patients In this section, one expects to find guidance on justification for the number of patients to be included. However, this is not mentioned and sample-size considerations should be addressed in this section. **Proposed change (if any):** Reconsider title of the section	
370		**Comment:** The abbreviation "ITT" is neither explained nor listed in the final Definitions. **Proposed change (if any):** Add the abbreviation "ITT" in the final Definitions.	
371-386		**Comment:** Section 6.1.2: Evaluation of activity It is stated that in the evaluation of ORR, the "ITT principle should be adhered to". The "ITT principle" is not defined in the Guideline. Also, the role of different analyses sets in different types of analyses is not clear, partly because the Appendix 1 section "Primary and sensitivity analyses" is not well cited in the core part of the Guideline. The ICH E9 Guideline that addresses this topic is not cited adequately. **Proposed change (if any):** Cite ICH E9 in the "Legal Basis" (Section 3) and the ICH E9 Section 5.2.3 on "Roles of the different analysis sets" in Appendix 1. Also, refer to Appendix 1 in the core Guideline at the relevant places where sensitivity analyses are mentioned	
548		**Comment:** The abbreviation "anti-CTLA4" is neither explained nor listed in the final Definitions. **Proposed change (if any):** Add the abbreviation "anti-CTLA4" in the final Definitions.	
565		**Comment:** The abbreviations "RcRn" and "IgG" are neither explained nor listed in the final Definitions. **Proposed change (if any):** Add the abbreviations "RcRn" and "IgG" in the final Definitions.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
733		**Comment:** The abbreviation "QoL" is neither explained nor listed in the final Definitions. **Proposed change (if any):** Add the abbreviation "QoL" in the final Definitions.	
743-789		**Comment:** Section 7.1.1 (Patient population) discusses Phase III trials whose targeting mechanism of action outweighs the heterogeneity arising from different indications. Recommend discussing this issue in the context of earlier and particularly of accelerated-development trials. a. This balance would need to be evaluated much earlier in the development programme b. If the targeting mechanism overcomes indication heterogeneity, it is very likely an accelerated approval path rather than the traditional Phase I/II/III path would be undertaken. **Proposed change (if any):**	
757		**Comment:** 'Patients are expected to be characterised by relevant tumour parameters' – it would be useful to specify the approach used to characterise (e.g. the type of instruments). It will also be useful to clearly specify what 'relevant tumour parameters' means. **Proposed change (if any):**	
790-837		**Comment:** Section 7.1.2: Reference therapy Whenever more than one reference regimen is used, stratification is recommended. It should be clarified that the stratification should be on the randomization as well as in the statistical analyses. It should be emphasized that in add-on studies, randomization is essential. **Proposed change (if any):**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
793		**Comment:** The term 'widely used' is ambiguous (could be 'widely used' in a developed country but not in a under-development country) **Proposed change (if any):** Define or clarify the term 'widely used'.	
804		**Comment:** (Section 7.1.2) The immediate context of the sentence beginning "In most cases" is that of non-inferiority, not superiority. **Proposed change (if any):** Omit or move the sentence that begins with "In most cases".	
806		**Comment:** (Section 7.1.2) Reference to section "7.6.3" should be "7.6.4" regarding non-inferiority studies. **Proposed change (if any):** Change "7.6.3" to "7.6.4"	
833		**Comment:** A better term instead of "cross-over" is given by "treatment switching" because it cannot be confused with cross-over studies. **Proposed change (if any):** Replace "cross-over" by "treatment switching" or add an explanation so that confusion with cross-over studies is avoided.	
834-835		**Comment:** Neither the guideline nor the referenced Appendix 1 contain criteria which have to be fulfilled for the exclusion of detrimental effects on OS. **Proposed change (if any):** Add criteria for the exclusion of detrimental effects on OS.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
841-847		**Comment 1:** Section 7.1.4: Randomisation and blinding It should be emphasized that even though blinding may not be possible or meaningful, randomization is essential. **Comment 2:** Suggest more detail about open-label trials, both in terms of acceptability and necessity, and additional steps to take. Suggest discussing degrees of blinding between "blinded" and "open-label", e.g. when treatment is known to patient sponsor can still potentially be blinded to summary evaluations of data, DMC can still potentially be used, central review can potentially be used and blinded for e.g. imaging assessments, etc. **Proposed change (if any):**	
848		**Comment:** Whether PFS and DFS are acceptable primary endpoints depends on the definition of progression and disease. **Proposed change (if any):** Add the condition that the definition of progression and disease has to be appropriate to use PFS/DFS as primary endpoints.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
848-929		**Comment 1:** Section 7.1.5: Endpoints When there is no medical justification for a certain endpoint but more than one is possible, statistical considerations should be taken. For example, for one possible endpoint the statistical power may be very low but for another possible endpoint the power may be high. Then this could be taken into consideration in the choice of primary endpoint. **Comment 2:** Section 7.1.5: Endpoints a. When it is not possible to assess progression at regular intervals, warranting a PFS rate at a fixed timepoint endpoint, PFS as a time-to-event endpoint can be calculated but this calculation may not be reliable. b. PFS2 endpoints – it is often infeasible to expect patients to return to the clinic for per-protocol tumor assessments following progression and treatment withdrawal, Time on next line therapy may be more likely to be the general case rather than the exception. In addition, it may be unreasonable to expect a PFS study to wait until PFS2 is mature before closing or reaching endpoint analysis. Suggest clarifying expectations. c. Suggest more detail about requirements for biomarkers of tumour burden, e.g. procedure and evidence needed to establish validity. **Proposed change (if any):**	
850-851		**Comment:** Whether prolonged PFS/DFS can be considered to be of benefit for the patient depends on the definition of progression and disease. **Proposed change (if any):** Add the condition that a patient-relevant definition for progression and disease is required to consider PFS/DFS to be of benefit for the patient.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
857-858		**Comment:** It remains unclear what is meant by "showing trends towards superiority". If just a not significant increase in OS is meant, this is insufficient to exclude relevant negative effects. **Proposed change (if any):** Add appropriate criteria (based upon non-inferiority testing) for the conclusion that there are no relevant negative effects on OS.	
1164-1168		**Comment:** Section 7.6.4: Non-inferiority studies The term "study sensitivity" is introduced. It should be recognised that in ICH/E10 the term "assay sensitivity" is used for the same, or very similar, purpose. Please consider to harmonise or explain the difference. **Proposed change (if any):** In ICH/E10 the term "assay sensitivity" is used for the same, or very similar, purpose than "study sensitivity". Please consider to harmonize or explain the difference.	
1168-1170		**Comment:** In section 7.6.4, the proposal "Similarly a per protocol analysis set should be defined" seems a bit weak, because a. presumably you expect it to be used in analysis, and b. restriction to a per protocol set introduces known biases which can be reduced by known methods, e.g. inverse probability of censoring weighting (*See: Colleoni M, Giobbie-Hurder A, Regan MM, et al. Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. 2011;29:1117-1124.*) **Proposed change (if any):**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
1172-1185		**Comment:** Section 7.6.5. Analyses based on a grouping of patients on an outcome of treatment Although imperfect and not addressing all sources of bias, a number of methods have been developed to address the relationship between survival and on-study events, including landmark analyses (Anderson et al., J Clin Onco 1:710-719, 1983; Anderson et al., J Clin Onco 26:3913-3915, 2008) and time-dependent covariate models, which could help alleviate the biases involved. **Proposed change (if any):**	
1302		**Comment:** The abbreviation "B/R" is neither explained nor listed in the final Definitions. **Proposed change (if any):** Add the abbreviation "B/R" in the final Definitions.	
1306-1315		**Comment:** It is correctly stated that bias is introduced if the collection of AEs is stopped at the time of study drug discontinuation or shortly thereafter. As the stopping of the documentation of adverse events when the study medication is discontinued is current practice, it should clearly be stated that this practice should be changed. **Proposed change (if any):** Add a clear statement that the documentation of adverse events should not be stopped when the study medication is discontinued to enable a fair comparison of treatment strategies.	
1327		**Comment:** Comparative studies for marketing authorisation should not only be recommended; comparative studies are mandatory. **Proposed change (if any):** Replace "recommended" by "mandatory" in the sentence "Therefore, whenever possible, comparative studies are recommended for marketing authorisation."	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
1365-1367		**Comment:** It is mentioned that time to event should play a role for key events. It should be more clearly stated that for time-to-event data, the application of appropriate survival time methods is required, which means that it may be necessary to deal adequately with competing risks and recurrent events. **Proposed change (if any):** Add a clear statement that for time-to-event data the application of appropriate survival time methods is required, which means that it may be necessary to deal adequately with competing risks and recurrent events.	
1369-1370		**Comment:** It is stated that "Time-adjusted analyses for AEs, e.g. incidence by different cut-off dates or event rates per 100 patient-years, may also be indicated if properly justified by the pattern of events." However, the justification to use event rates per 100 patient-years is the strong assumption that the considered endpoint follows an exponential distribution, which is frequently questionable. For descriptive purposes, event rates per 100 patient-years may be useful, but the corresponding statistical inference (significance tests, confidence intervals) requires the exponential distribution, which is frequently not the case. **Proposed change (if any):** Add a more clear-cut guidance on the use of event rates per 100 patient-years including a statement that the justification for statistical inference for event rates per 100 patient-years is given by the exponential distribution, which, however, is rarely valid in practice.	
1455-1456		**Comment:** It is stated that "Modelling and simulations may provide complementary information where data in (parts of) the paediatric population are difficult to obtain." It should be clearly stated that modelling and simulations are no substitute for empirical comparative data. **Proposed change (if any):** Add a clear statement that adequate empirical comparative data are required to demonstrate the safety of anticancer medicinal products.	

Please add more rows if needed.