European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH CANCER CHEMOTHERAPY

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

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	
2	MSD	
3	ProStrakan	
4	Schering-Plough	
5	International Biometric Society (IBS)	

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Table 2:Discussion of comments

GENERAL COMMENTS	
Generally, the guideline is well written and provides clear and relevant guidance on the non-clinical and clinical development of medicinal products for the treatment of nausea and vomiting associated with cancer chemotherapy. We consider that the principal aim of the development of any potential medication in this indication should be prevention. Control of nausea and vomiting during the acute phase is one of the major determinants of the incidence and effective management of delayed nausea and vomiting [Roila, 1997; Ossi, 1996]. Thus, the adequacy of the management of nausea and vomiting in the acute phase should be borne in mind when evaluating clinical data on the management of delayed nausea and vomiting. As the principal factor in the management of acute nausea and vomiting is prevention, not treatment, prevention of nausea and vomiting should be the principal aim of the development of any potential medication in this indication. EFPIA	Fully endorsed. The title has been revised (from ”treatment” to “prevention)”
Propose: • Add a table reviewing and defining the many acronyms contained within the guideline • It should be useful to define more clearly the following terms: nausea; emesis • Add a bibliography appendix • The paragraph "2.1 General Considerations" should be removed from the part "2. Non-clinical development", as its content is general and includes some clinical points. It should therefore be placed as an independent part. EFPIA	Included Defined in clinical guidelines References are not included in Notes for Guidance documents Paragraph revised and now covers only non-clinical issues.
This document seems to refer only to full development programmes for new chemical entities with no reference to “abridged” programmes for re-formulations. A more complete definition of what the agency mean by “a new product” may help reduce any ambiguity. ProStrakan	It is correct that the guideline refers to full development for new chemical entities, as does most clinical guidelines.
There is a lack of guidance regarding development of medicinal products to treat nausea and vomiting associated with chemotherapy given over multiple days. ProStrakan	Multi-day chemotherapy is only mentioned in 3.2. “Patients receiving multi-day chemotherapy are at risk for CINV on days of and subsequent to chemotherapy. The period at risk for CINV after the end of a multi-day regimen depends on the specific regimen and mainly on the emetogenic potential of the chemotherapy agents administered late in the regimen.” However, the guidance with respect to endpoint, optimisation of posology, etc. apply.

SPECIFIC COMMENTS ON TEXT

1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Paragraph 1 p. 2/8 MSD, EFPIA	Although CINV occurs after many chemotherapeutic regimens, is it the 'most frequently reported adverse event'? **Propose:** addition of 'one of the most' (Line 1 in the Introduction).	Revised as proposed
Paragraph 2 p. 2/8 MSD, EFPIA	"The pathophysiology of CINV is not well understood..." EFPIA believes that, relative to other complications of chemotherapy (e.g. fatigue, asthenia), the pathophysiology of chemotherapy induced vomiting is quite well understood. **Propose:** Modifying the wording to read: "it is complex and ..."	Revised as proposed
	The CTZ is chemoreceptor trigger zone (not chemotherapy receptor trigger zone). The areas involved in the co-ordination of nausea and vomiting are a group of nuclei often referred to as the dorsal vagal complex. **Propose:** Rephrasing Line 7 as follows: "Mechanisms involved include activation of the chemoreceptor trigger zone (CTZ) and/or the nuclei in the dorsal vagal complex directly or indirectly..."	Revised as proposed
	Although cortical mechanisms may contribute to emesis (anticipatory nausea and vomiting), we are not aware that vestibular mechanisms have been conclusively implicated in CINV. Certainly disruption of the vestibular system can lead to nausea and vomiting particularly in motion-induced emesis, vertigo and labyrinthitis. **Propose:** Removing 'vestibular' such that the sentence reads: "In addition cortical mechanisms may contribute particularly in anticipatory nausea and vomiting which are known to occur in patients receiving multiple cycles of chemotherapy."	Revised as proposed

2 NON-CLINICAL DEVELOPMENT		
2.1 general Considerations		
Paragraph 2 p. 2/8 MSD, EFPIA	Preclinical assays are not yet available and characterised to allow assessment of the persistence of anti-emetic activity following repeated cycles of chemotherapeutic agents. As a result the assays would need to be established AND we would then need to relate them to clinical findings. Ethical issues would also have to be overcome in most countries regarding the administration of repeated doses of the agents used clinically to treat cancer. The doses that would typically be used in preclinical studies are high (cisplatin is 100-200 mg/m2 in ferrets) and would have significant morbidity if administered repeatedly. Further the assay in ferrets that has been used most recently to assess anti-emetic effects against acute and delayed phases of emesis has only been routinely used with cisplatin as the emetogen. **Propose:** Requirement for testing anti-emetics preclinically following multiple cycles of chemotherapeutic agents is removed.	Revised as proposed
Schering-Plough	It would be helpful to have some guidance as to the need for chronic tox. studies and/or carcinogenicity studies.	These issues are covered by general non-clinical guidelines. Chronic tox. studies should cover the expected duration of therapy (repeat use) while carcinogenicity studies are not required for this indication.
Paragraph 2 p. 2/8 EFPIA	The basis for the request to perform a comparison to other compounds with known effect on the intended mechanism is not understood. Cisplatin is the only chemotherapeutic agent used in animals. **Propose:** Clarification on the "*other compounds*".	Revised in order to clarify the meaning: "Studies investigating site of action (central and/or peripheral) are encouraged and may, for example, include known centrally acting compounds (e.g. morphine, apomorphine)." The advice to include also other cytotoxic compounds than cisplatin as emetogen is retained.
Paragraph 4 p. 3/8 EFPIA	**Proposal:** Request clarification for the following points which are considered unclear: - "*Pharmaceutical interactions with the human target"* - "*Interaction with human protein"* Which kind of human protein is intended in this sentence? Are receptors also concerned? - "*Early panel screens"*	Paragraph revised: "The affinity/activity of the compound with the human target receptor should be characterised *in vitro*. Consideration should be given to the activity of the corresponding animal homologues from the species to be used for *in vivo* studies. An early receptor panel screen as general background information to address the specificity of the compound should be performed."

Paragraph 5 p. 3/8 EFPIA, Schering-Plough	The measurement of cognition in preclinical assays is problematic because performance in these tests may be compromised by many effects of test compounds. Thus assays that use food rewards may be affected by drugs that affect appetite. Sedation and motor incapacitation can be assessed preclinically but at doses which produce no effect in these assays it is still regarded that the animal's ability to carryout a complex motor task may be compromised (e.g. some cognitive assays require pressing of a lever). **Proposal:** preclinical assays are not considered the most appropriate way to assess cognitive disruption	Paragraph revised, "cognitive disturbances" deleted
Paragraph 5 p. 3/8 EFPIA	This request has no interest for a product with a peripheral effect. Is it requested to check that there is no CNS effect for a product with a central effect? **Proposal:** Further clarification for the request.	Paragraph revised, qualifier added: "especially for centrally acting compounds"
Paragraph 7 p. 3/8 MSD EFPIA	The possibility of interactions between the anti-emetic drug and the anti-tumour activity of chemotherapeutic agents is problematic to explore preclinically due to the poor predictive value of assays that are currently available. The value of in vivo murine tumour assays in this context is debatable. **Proposal:** This requirement is removed. We do not understand the objective of the pharmacodynamic interactions that are requested. The request to conduct "*interactions studies in vitro*" which are advisable for compounds where non-clinical and clinical data are sparse, is also unclear and needs to be clarified. It is not possible to study both anti-tumour and anti-emetic effects in animals especially because the studies with tumour bearing animals are very specific and only performed in mice and rats and not possible in pigs or ferrets.	The possibility of a pharmacodynamic interaction between the anti-emetic agent and chemotherapy should be addressed. How to do this partly depends on how well-defined the pharmacology of the anti-emetic agent is. It is correct that the predictive value of murine tumour assays is debatable and this is similarly true for *ex vivo* cytotoxicity assays. Nevertheless, if there are no signals in a comprehensive preclinical package, clinical studies addressing this issue are not needed from a regulatory perspective There is no need to investigate the anti-emetic activity of the experimental compound in tumour bearing animals.

2.2 In vivo models of chemotherapy-induced emesis		
p. 3/8 MSD, EFPIA	Ferrets appear to be the species with the greatest predictive value for anti-emetics to be used in humans. Increasingly house musk shrews (Suncus murinus) are used in preference to dogs for emesis studies. **Proposal:** House musk shrews are used together with ferrets.	Revised in line with the proposal
p. 3/8 MSD, EFPIA	Although foot tapping in gerbils has been used as a means of assessing in vivo activity of a specific class of receptor antagonists (that is NK1 receptor antagonists) they are NOT a model or assay of emesis. **Proposal:** Removing 'foot tapping in gerbils' from the last line of page 3. In addition, Pica in rats has been reported recently to have little value (Rudd et al. Eur J Pharmacol. 2002 454:47-52.) **Proposal:** Removing 'drug-induced pica in the rat'.	Revised in line with the proposal
Paragraph 1 p. 3/8 MSD, EFPIA	Pre-clinical studies performed with cisplatin are considered sufficient and that repeated studies with some other products, for which the active doses leading to emesis are not known, would not be useful and should not precede a first administration into man. **Propose:** Replace the term "*recommended*" with "*possible*" in the last sentence of the paragraph in order to read " "*The anti emetic activity … or ifosfamide are* **possible**.*"*	Revised in line with the proposal
Paragraph 2 p. 3/8 MSD, EFPIA	Based on the available data from the literature and on the studies performed only with the ferret for aprepitant (Emend). **Propose:** Replace the words "*in several species*" by *" in one specie such as dog, pig, ferret, musk shrew or pigeon*" in order to read "*The standard approach is the drug-induced emesis in* **one specie such as dog, pig, ferret, house musk shrew or pigeon**.*"*	Revised in line with the proposal
Paragraph 3 p. 3/8 MSD, EFPIA Schering-Plough	**Propose:** As proposed for pg3 above, removing "*… foot tapping in gerbils*" and "*Drug-induced pica in the rat*" cannot be considered as an appropriate model and should be replaced by another appropriate one. Proposed revised wording: Other approaches of demonstrating activity at the target site using scientifically established models can be considered, such as drug induced pica in the rat	Revised in line with the proposal See above

3. CLINICAL ISSUES		
3.1 Background		
MSD	The issue of classification of emetogenicity of chemotherapy regimens is complex. It is no longer possible to assess emetogenicity of single agents or regimens rigorously because of the widespread use of antiemetic prophylaxis - the original classifications were done in patients who received either no prophylaxis or placebo prophylaxis. A new approach is needed based on data derived from patients who do receive some antiemetic prophylaxis. Also, it does not make sense to classify emetogenicity during the acute phase only - the entire period (5 days) during which patients are at high risk should be assessed. MSD suggests noting on page 4 that *"In light of the arbitrary nature of acute and delayed the entire period (i.e. 5 days) during which patients are at high risk should be assessed."* We further believe that less emphasis on 'acute' and 'delayed' emesis should be made throughout the document given the arbitrary nature of these definitions.	It is agreed that the entire period at risk should always be assessed. The primary objective of a trial might be, however, to improve the outcome with respect to, e.g. acute CINV or cisplatin-induced delayed CINV and this is considered acceptable.
Paragraph 4 & 5 p. 4/8 EFPIA	Paragraph 4 begins by listing a number of agents for the treatment of CINV, including the most commonly used agents and a recently marketed novel agent. Although the use in clinical practice of this novel agent, a neurokinin 1 receptor antagonist, is to be determined, the current text is confusing as to which (commonly used *versus* marketed) product is considered the more appropriate comparator in demonstrating efficacy. **Propose:** The most commonly used agents in the treatment of CINV are 5-HT_3 receptor antagonists, glucocortoicosteroids and dopamaine receptor antagonists. ~~Recently, a new antiemetic agent (aprepitant), an antagonist of the neurokonin 1 (NK1) receptor, was marketed for the prevention of CINV.~~ All compounds have at least some activity against acute CINV, while currently only corticosteroids and the recently marketed neurokinin 1 receptor antagonist aprepitant have well documented activity against cisplatin-induced delayed emesis. The choice of a single or a combination antiemetic regimen, as well as the duration of treatment, should be based on the emtogenic potential of the chemotherapeutic regimen and used in accordance with recognized treatment guidelines (see Section 3.4.3 Main efficacy studies).	Revised as proposed As pointed out by EFPIA, treatment guidelines are referred to in section 3.4.3. This is considered sufficient.

Paragraph 6 p. 4/8 bullet 2 EFPIA	In understanding the risk and benefit associated with the prevention and treatment of delayed emesis, it is essential to define more clearly what is meant by "delayed emesis" to avoid confusion. An old definition of delayed emesis illustrated in Figure 1 is "nausea or vomiting beginning 24 hours or more after chemotherapy administration" [De Vita, 1993]. This is a distinct situation, occurs in a minority of patients and is very uncommon with drugs other than cisplatin. This type of delayed emesis arises when the acute emesis following chemotherapy has begun to settle and an entirely new episode of emesis begins. The mechanism of this delayed-onset emesis is unknown, and the emesis is intractable to therapy (with dexamethasone, 5-HT3 antagonists, NK-1 inhibitors or any other class of anti-emetic). More recently, "delayed emesis" has been defined as "vomiting occurring 24 hours after chemotherapy" [ASCO Guidelines, Gralla R, JCO, 1999]. In other words, this is the simple continuation of the acute emesis and could be regarded as "prolonged acute emesis". This type of delayed emesis is illustrated in Figure 2 and is eminently treatable. The study was a comparison of two different doses of palonosetron (a long-acting 5-HT3 antagonist) to a single dose of ondansetron in patients scheduled to receive moderately emetogenic therapy. The results are a clear demonstration of the efficacy of 5-HT3 antagonists in the management of delayed emesis. However, because the ondansetron was not repeated on day 1 and not given at all on days 2, 3 and 4 (which is not how the drug is used according to the extant treatment guidelines or registrations), no conclusions can be drawn about the efficacy or otherwise of ondansetron in the management of delayed emesis. This more recent definition has gained international acceptance [MASCC Guidelines, 2002] and is now used routinely in the clinical development of anti-emetic therapies for chemotherapy-induced nausea and vomiting.	The wording has been revised: "Chemotherapy-induced nausea and vomiting can be broadly categorised as: • *Acute*: occurring within 24 hours of therapy • *Delayed*: occurring more than 24 hours after administration of chemotherapy and persisting for up to 5–7 days • *Anticipatory*: occurring prior to the administration of chemotherapy and in patients with poor control of CINV during previous cycles of chemotherapy. This classification is partly arbitrary. In the typical case of cisplatin-induced emesis, the delayed phase commences around 16-18 hours after cisplatin administration and after a period of relative quiescence, while in the case of high-dose cyclophosphamide, e.g., there is no clear delineation between early and delayed emesis. Delayed emesis may in the latter case be regarded as prolonged acute emesis. Irrespective of these differences, this terminology differentiating between "acute" (≤24 h) and "delayed" (>24 h) CINV has gained general acceptance in the medical community and is also accepted from a regulatory perspective."

Paragraph 6 p. 6/8 MSD, EFPIA	In certain clinical settings outside oncology, re-randomisation may be appropriate - e.g. migraine. Re-randomisation prior to the second cycle of chemotherapy may provide interesting scientific information, however the aim of antiemetic therapy in the context of cancer patients receiving chemotherapy is to prevent symptoms throughout the entire course of chemotherapy. This is why few if any trials using re-randomization have been done in this clinical setting and such trials would be ethically problematic using agents of established antiemetic efficacy. **Propose:** The need for re-randomisation should be deleted.	There is a carry over effect between cycles of chemotherapy related to control of emesis in prior cycles. In order to address this, re-randomisation is recommended in at least one trial. Such a trial should be viewed as complementary to trials not using re-randomisation. The ethical concerns related to re-randomisation are not well understood ("would be ethically problematic using agents of established antiemetic efficacy").
3.4.3 Paragraph 2 MSD	Standard therapy should be based on accepted treatment guidelines for instance. Now that an NK1 receptor antagonist has been established as a necessary component of standard antiemetic therapy for patients being treated with highly emetogenic chemotherapy according to the recommendations of the international cancer supportive care organization (MASCC), future trials of novel antiemetic agents will need to use a comparative regimen that conforms to the MASCC recommendations for ethical reasons.	From a regulatory perspective, non-inferiority trials vs. an NK1 receptor antagonist (as add-on to standard therapy) might be less informative than superiority studies vs. placebo (as add-on to standard therapy). The ethical aspects are acknowledged, however, and treatment guidelines and general clinical uptake of new treatment principles are both of importance with respect to the need for comparative data. By necessity this refers to a dynamic field. Therefore it is considered inappropriate to mention specifically one medicinal product.
3.2 Study Populations and Chemotherapy Regimens		
p. 4/5 EFPIA	**Propose:** The study populations mentioned should be completed by a paragraph on specific populations of phase I studies, as healthy subjects.	Healthy volunteers are mentioned in 3.4.1 (PK studies)
IBS	Add tumour stage	Revised in line with comment
IBS	The restriction to "patients receiving multi-day therapy" seems somewhat confusing as the rest of the paragraph fits all types of regimens.	Revised in line with comment
Schering-Plough	We appreciate the openness that is being allowed on using subsequent cycles to explore regimens and non-responders and would like to see that section expanded in the final guidance.	There is currently very limited regulatory experience with respect to drug development with a labelling claim, e.g. as regards patients with CINV refractory to prior standard therapy. In case such development is considered meaningful, regulatory scientific advice is recommended.

Paragraph 2 p. 5/8 EFPIA	**Propose:** providing the Hesketh Scale as an appendix. To our knowledge, the current guidelines used for the clinical development for anti-emetic products are those from the FDA and from the Multinational Association of Supportive Care in Cancer (MASCC). We have not found the modifications and amendments of the Hesketh Scale and we are confused with the following last sentence "*they may used **if** generally recognised"*. **Propose:** more precise information on the guidelines to be followed	As the Hesketh Scale might be further refined in the future, it is considered appropriate just to refer to the update of 2005 Further modifications are foreseen of these scales, but the sentence "they may be used if generally recognised" has been deleted.
Paragraph 5 p. 5/8 EFPIA	The recommendations are unclear. We do not know if we have to specify the chemotherapy in inclusion criteria or base the inclusion on the Hesketh classification. **Propose:** Greater precision on the recommendations.	Wording revised: "From a regulatory perspective it is acceptable to use a restricted number of predefined regimens falling within the same emetogenic risk category for the documentation of the treatment effects as regards acute CINV."
ProStrakan	How should the broad use of glucocorticosteroids in clinical practice be addressed in clinical studies ➢ They are recommended standard of care ➢ They are used in high doses with other medications (taxanes) ➢ They are used in high dose in certain tumour types	It is advised that studies should be designed in a way that ensures that the use of glucocorticosteroids is balanced between treatment arms.
3.3 Methods to Assess Efficacy		
Paragraph 1 & 2 p. 5/8 EFPIA	Please clarify why "*retching"* is mentioned as it cannot be evaluated.	Retches/dry heaves can be reported and may be observed.
Paragraph 3 p. 5/8 EFPIA	We do not agree with the choice of the primary endpoint "*absence of emesis <u>and</u> nausea*" as nausea is not quantifiable. In our opinion, the primary endpoint to be used is complete response: "*absence of emesis and no medication rescue*" which is the current standard primary endpoint used in the aprepitant (Emend) clinical studies.	Nausea is considered quantifiable. "Absence of emesis and no medication rescue" is put forward as an alternative responder definition in the revised document.
Paragraph 6 p. 6/8 Schering-Plough	Many agents improve emesis or nausea without necessarily improving both. We rather suggest flexibility in the endpoints, with the understanding that the endpoint used will determine the indication(s) allowed in the label	Se above. For example, add-on therapy aiming at improving nausea in a setting where standard therapy achieves control of emesis would be possible. As this would be a new therapeutic claim from a regulatory perspective, regulatory agreement in advance may be considered.
Paragraph 6 p. 6/8 MSD, EFPIA	A clarification is requested for the recommendation made for "*re-randomisation prior to the second cycle of chemotherapy"*.	See above

Paragraph 7 p. 6/8 EFPIA	It is not clear why proportion of subjects with CC during the "*full risk period*" should be evaluated as a secondary endpoint, when this would appear to be the proposed primary objective.	Revised wording: **"**Depending on the objectives of the study, CC or R during the first 24 hours after chemotherapy or for the full period at risk, e.g. 5 days may be used as primary end point for main efficacy trials. Also if the aim is to improve acute CINV, results for the full period at risk should be reported and at least non-inferiority demonstrated."
Schering-Plough	The guideline is inconsistent in referring to the delayed phase – in some places it states 5-7 days, in other 5 days.	In most cases "e.g." is stated. The main message is that the full period at risk should be covered in the assessment of efficacy
ProStrakan	A distinct definition of end-points would help ensure continuity i.e. Complete Response/Complete Control	The text has been revised in order to provide more precise guidance.
3.4.1 Pharmacokinetics		
p. 6/8 EFPIA	Please define the acronym ANC ("kinetic and/or dynamic data such as ANC")	"absolute neutrophil count" is now used instead of ANC
Paragraph 3 p. 7/8 EFPIA Schering-Plough	It is important to note that practically, patients with hyperbilirubinemia are excluded from the clinical studies and it would be very difficult to assess these patients in prior to the initiation of the confirmatory studies.	Agree, paragraph deleted
3.4.2 Therapeutic exploratory studies		
Paragraph 3 p. 7/8 last sentence EFPIA	The last sentence *"The benefits of the experimental compound…should be investigated"* should be clarified.	Sentence deleted. Revised wording: "Randomised exploratory, add-on or substitution trials (see below) using a generally recognised regimen as reference are recommended in order to optimise the posology of the experimental compound."
Schering-Plough	The suggestion that dose finding studies may be conducted as monotherapy is not acceptable to many ethics review boards. Also in this section it is indicated that early studies may be conducted in patients treated with chemotherapy regimens of low emetogenic potential.	The problems related to use of an experimental agent as monotherapy are acknowledged. This is also the reason why chemotherapy regimens with low emetogenic potential are mentioned here. Wording slightly revised: "Early monotherapy studies may be conducted in patients with regimens of rather low emetogenic potential in order to define active dosages to bring forward to studies in patients undergoing more emetogenic therapy."
3.4.3 Main efficacy studies		
p. 7/8 EFPIA	The treatment guidelines should reflect the value of properly conducted meta-analyses in evaluating therapies in this indication.	There is no specific role for meta-analyses in CINV. Please refer to CPMP/2330/99 Points to Consider on Application with 1.) Meta-analyses and 2.) One Pivotal study.
p. 7/8 EFPIA	Please define the acronym PtC ("ref. PtC on the choice of non inferiority margin")	The Points to Consider document is now adopted and named "Guideline", text revised
IBS	The preference of studies in patients receiving highly emetogenic	It is believed that the need for new compounds is most pronounced in

	regimens may be questionable. In practice this refers to cisplatin-based regimens. However, cisplatin has lost its dominant role in several major tumour indications.	patients undergoing highly emetogenic chemotherapy. It is agreed that if not the aim is to specifically investigate effects on cisplatin-induced delayed emesis, the study may, perhaps preferably, be conducted in relation to cisplatin-free highly emetogenic regimens.
IBS	If a formal proof of conserved antitumour activity of every chemotherapy regimen is required, the option "non-restricted indication" or "extrapolation" is not realistic. What about the same chemotherapy regimen in different tumour indications? Is it necessary to show unchanged antitumour activity for every tumour type?	It is foreseen that in most cases, non-clinical/pharmacological data are sufficient to exclude with reasonable certainty a pharmacodynamic interaction with chemotherapy. The design of clinical studies should be mechanistically guided. If, for example, a general tumour protective effect cannot be excluded, i.e. effects not mechanistically related to a specific class of chemotherapeutic agents, it is sufficient to show absence of a relevant effect on tumour response in a clinical study designed in line with the guidance given in the document. Extrapolation, etc. is foreseen as possible.
Paragraph 3 p. 7/8 EFPIA Schering-Plough	The assessment of tumour response rate has not been previously done in antiemetic trials because of the heterogeneity of the patient populations - different diagnoses and different staging and is therefore unlikely to provide meaningful information. **Proposal:** Delete the need for assessment of tumour response should be deleted.	The comment from EFPIA/Schering-Plough is factually/historically correct. The wording in the guideline is nevertheless considered appropriate: "If it cannot be excluded with reasonable certainty (see 2.1) that the experimental compound may show a relevant dynamic interaction with chemotherapy as regards anti-tumour activity, the confirmatory studies programme should be planned to assess that possibility. Therefore a defined chemotherapy regimen in a homogenous population of patients with a defined and chemosensitive disease should be chosen and the number of patients should be justified also from an anti-tumour activity perspective. Response rate is an acceptable measure of anti-tumour activity."
Last paragraph p. 7/8 EFPIA	It is not clear why studies with moderately emetogenic therapy are emphasized for compounds added to standard therapy. As the standard therapy is not necessarily the same for highly and moderately emetogenic therapy, a clarification about this request is needed.	The wording has been revised: "In cases where relevant add-on activity to a standard regimen has been demonstrated in patients undergoing highly emetogenic chemotherapy, it cannot be postulated that the experimental compound will show relevant add-on activity in case of moderately emetogenic therapy, even if the same standard regimen is used also in these patients. In order to support claims, studies specifically addressing this issue are expected. If, however, at least non-inferior activity has been shown in a substitution study in case of highly emetogenic therapy and the use of the standard regimen is well documented also in moderately emetogenic chemotherapy, extrapolation as regards activity might be feasible, but

		should be justified."
Schering-Plough	It is questioned why "non-inferiority are likely to be the rule" when non-inferiority trials will mean 800+ patients as opposed to superiority trials (add-on) which will mean 300+ patients.	Paragraph deleted. See also comment 3.4.3, paragraph 2 above. If non-inferiority trials are undertaken, the general guidance as regards these trials with respective to "assay sensitivity" should be adhered to.
Schering-Plough	The present guidance does not provide pathways to approval based on reduction in adverse reactions or reduction of drug interactions.	This is correct and constitutes an issue in most therapeutic areas and was therefore not specifically mentioned here. Safety advantages, for example, may be used in order to justify acceptance limits as regards non-inferiority in terms of efficacy.
3.4.4 IBS	The recommendation of studies that include patients above the age of 75 may be problematic as a high proportion of these patients will not be treated with aggressive chemotherapy.	Also elderly patients are treated with emetogenic chemotherapies, albeit less frequently with highly emetogenic cisplatin-based regimens. Please also notice the wording (inclusion of elderly) "is encouraged".