Guide for Assessors of Centralised Applications for the Assessment of SmPC section 5.1

1. General comments on 'Assessment of SmPC section 5.1 A guide for Assessors of Centralised Applications'

	Stakeholder name (*to be repeated in all rows*)	General comment
	MAJOR COMMENTS	
1	EFPIA	**1.** Overall, our interpretation of the draft guideline is that its **more restrictive** in terms of what EMA has allowed for inclusion in section 5.1 up to now. While removal of repetitions is considered beneficial, there is a shift from providing minimal clinical context to mainly including numbers without the important additional clinical context. While the SmPC is directed to prescribers and HCPs, the EMA appears to **focus on prescribers only**. The overall objective of the assessors' guide appears to be to **shorten section 5.1.** Little consideration is given to a balanced representation of relevant data for decision-making (for prescribers AND HCPs). In this context, **patient relevant evidence** should be considered. The focus on statistically compelling information may lead to a disadvantage re information relevant for small populations, e.g., paediatric patients, elderly patients, orphan diseases, gender specific information.
2	EFPIA	**2.** Section 6 of the draft guide seems very clinician-focussed and focusses too little on the patient voice. There is a need for inclusion of outcome measures in clinical trials that are patient relevant and patient data is needed to generate evidence of meaningful outcomes for patients. This is supported by EMA as worded in the summary of the workshop "Patient experience data in EU medicines development and regulatory decision-making" (EMA/354012/2020). See specific comments on PRO section. We advocate for **a PED explicit mention in SmPC, including, but not limited to PRO**. Is there an opportunity for clarification around the acceptability of PROs in open label study with pre-specified analyses to control for bias?
3	EFPIA	**3.** We recognise the role of both randomised controlled trials (RCTs) and RWE as providing complementary evidence to support benefit/risk decision-making. Therefore, where **RWE i**s supporting a positive benefit/risk decision, the results should be reflected in section 5.1 of the SmPC to optimally assist the prescriber's decision whether the benefit/risk of treatment can be expected to be positive for a specific patient.
4	EFPIA	**4.** The document gives **general recommendations about what results to share with HCP** that may be inconsistent with (a) pre-specified analyses designed to inform HCP, or (b) analyses that supported the rationale for approval with multiple stakeholders. Therefore, we are concerned about **re-interpretation** of findings that may go against the goals

		of a development program, that went through pre-specification, study design, scientific and regulatory advice at the planning stage, and review of findings, to ensure clinical relevance of the results. For example, • the ICH E9 Addendum lists five possible strategies and recommends tailoring the **estimand strategy** to the clinically relevant question, justifying it, pre-specifying it and letting that strategy guide the design, analysis, and reporting. Yet, Section 6.3 Estimand of the document endorses the treatment policy strategy as "most valuable for regulatory decision making" in general terms. • Similarly, clinical considerations often justify the **selection of primary and secondary endpoints**, and the hierarchy of testing in the development program. Yet, Section 6.4.1 seems to re-visit that thinking in favour of what the reviewer deems clinically relevant or statistically compelling for HCP. • Also, the recommendation against sharing **comparisons to external or historical control groups** in Section 6.4.10 on Single arm trials may go against important information supporting approval or interpretation of results when for example the historical control group gives information on a poorly understood natural history of a rare disorder. **Recommendation for change:** Suggest that the document clarifies that as a default, the summary of findings for HCPs shall be consistent with the scientific rationale for approving the product, summarizing, or translating those findings to HCP when necessary. Therefore, while re-interpretation of findings from a development program in a manner that is inconsistent with the pre-specified analyses plans or inconsistent with the rationale for approval is possible, such re-interpretation should be justified and be the exception rather than the default.
5	EFPIA	**5.** **External control data**: We acknowledge the difficulties to contextualise the treatment effect based on external or historical data. However, not providing any **contextualization of results** could lead to an incomplete, and therefore biased, understanding of the trial outcome and results by HCPs and patients. We recommend that a contextualization of the treatment effect based on external or historical data should be provided with a cautionary statement to clarify the limitations of interpretating such data. Suggestions for changes are provided in the specific comments.
6	EFPIA	**6.** The purpose of the document is to provide guidance to assessors of the SmPC in terms of the information to include in 5.1. Yet, the document **seems in various parts to provide methodological guidance**. Some of this guidance is controversial, if not even in conflict with existing CHMP guidelines. Since such methodological advice is out of scope for this guidance, we recommend removing them from this document. For example, paragraphs 2 and 3 in Section 6.3 seem to imply that a treatment policy estimand should be used 'most often' in confirmatory trials. Such advice:

		a) goes beyond the scope of this document, b) is not aligned with existing CHMP guidelines (e.g., EMA/CHMP/ICH/436221/2017 which is neutral about the choice of estimands or CPMP/EWP/1080/00 Rev.2 which suggests a hypothetical estimand), and c) is, in various settings, doubtful (e.g. in non-inferiority or equivalence trials) or even unreasonable (e.g. in the case of death being an intercurrent event, as clarified in Section A.3.2 of EMA/CHMP/ICH/436221/2017). Other examples are provided in the specific comments below.
7	EFPIA	**7. Estimand language in guideline :** While the guideline has a section on estimands, outside this section the guideline is written as if CHMP guideline EMA/CHMP/ICH/436221/2017 would not exist. For example, the term intercurrent event is not used in the document even though it discusses for example treatment and study discontinuations, missing data, composite endpoints...
8	EFPIA	**8.** Clarify if this Guideline **will be applied prospectively** e.g., to new SmPC section 5.1 content and when other parts of existing section 5.1 of the SmPC are being updated.
	OTHER GENERAL COMMENTS	
9	EFPIA	The Summary of Product information is intended to be kept up to date with current scientific knowledge. Hence, relevant studies related to the approved indication under Section 5.1. provide valuable information to the prescriber and **should be included throughout the lifecycle**.
10	EFPIA	The Guideline should take into consideration and consistently reflect the guidance and examples given in other EMA online resources e.g., presentations provided by the SmPC Advisory Group on how to write and prepare an SmPC. There are instances where the examples given in these resources are not consistent with the proposed draft Guideline
11	EFPIA	**(12-106)**: Suggest **Pharmacotherapeutic group and ATC code** be mentioned here. Rationale: These are also required for section 5.1. Proposed changes: The SmPC Guideline [1, pp. 19–20] describes the following 5.1 subsections: **• Pharmacotherapeutic group: {group}, ATC code**: • Mechanism of action (if known) • Pharmacodynamic effects • Clinical efficacy and safety • Paediatric population

(Add more rows as needed)

Specific comments on text

2. Introduction

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	**2.1 Problem Statement (52)**: "Prescribers" may have to be replaced with "Prescribers and other health care professionals." as relevant throughout the document. Information in SmPC in particular section 5.1 is becoming more important for other stakeholders than just HCP, therefore what is allowed in Section 5.1 should also take into account the needs of for example HTA for which the joint clinical assessment will be implemented in the future Rationale: [1, p. 19] includes "other health-care professionals" and is not limited to prescribers. Therefore, consideration may be given to other readers of an SmPC, such as nurses and experts in joint clinical assessments of health technologies. In order to avoid misunderstandings in the sections following 2.1 of the guide, the term "prescriber" may generally be replaced by "**reader**" (e.g. as done in section 6.4.3). Proposed change:1) “The SmPC is a key information source for prescribers **and other health-care professionals (referred to as “reader” for the remainder of the guide).”**
2	EFPIA	**2.1 Problem Statement** (**53-55**): This may have to be a balanced statement. Proposed change:“~~However~~, **While** too much text is contrary to the principles of brevity and conciseness, as recommended in the EC SmPC Guideline in agreement with the CHMP. [1, pp. 19–20], **relevant information needs to be provided for readers to help guide decision making.**

(Add more rows as needed)

3. Principles of the regulatory framework of 5.1

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	**3.1 What is it for? (67 and 68)**: It is recommended that the guideline acknowledges the broader range of use of the SmPC by other stakeholders. Proposed change: **It is also the reference document to be used for any advertisement related to the product [3, Art 87], as well as reference document for other stakeholders, e.g. Reimbursement discussions.**
2	EFPIA	**3.2 Scope of 5.1 (74)**: It would be helpful to understand how the new approach to section 5.1 will be applied moving forwards i.e., will it apply only to newly authorised medicinal products or will already authorised medicines be subject to revision at the next opportunity? Depending on when/how the new approach to section 5.1 is applied this could create discrepancies between different medicinal products authorised in the same indication (with older, existing products having potentially more information and details in section 5.1 than newer products, assuming that the section 5.1 guidance is applicable moving forwards).
3	EFPIA	**3.2 Scope of 5.1 (74)**: Suggest rewording: "Section 5.1 should be **in general** limited to the indication". What about the situation where Clinical Trial Arms included different dosages?
4	EFPIA	**3.2 Scope of 5.1 (74 -76):** Examples should be included here on instances where it may be acceptable to include in the SmPC information on clinical trials in an unapproved indication, such as e.g., where there is a specific risk or where there is known off-label use. These examples and guidance are included in the 'How to review and prepare an SmPC' resources on the EMA website and so should be consistently reflected within this Guideline.
5	EFPIA	**3.2 Scope of 5.1 (74-76)**: while the concept of "posology" is included in the first sentence, it appears to be missing from the second sentence. Please add "posology" as highlighted in bold: "Section 5.1 should be limited to the indication, target population and posology that are authorised. No information should be given on indications/**posology**/populations that were not applied for or were rejected (except for paediatrics).

6	EFPIA	**3.2 Scope of 5.1 (81-82):** Please clarify Unclear if they consider relative figures to be optional and only absolute figures to be must haves. The magnitude of effects should be described using absolute and relative figures
7	EFPIA	**3.2 Scope of 5.1 (83)**: Subgroup analysis are not always necessarily limited in robustness. E.g., these could be pre-specified in the protocol, conducted in a hypothesis-driven manner, etc. Meta-analysis of 2 studies could also strengthen the quality of evidence. Make it clear in the guidance how robustness should be presented (e.g., should we start presenting p-value, CI or other measures to reflect quality of evidence of subgroup or post-hoc analysis?)
8	EFPIA	**3.2 Scope of 5.1 (83)**: In the italics, the words “clinically relevant” are used, yet in line 131 the instruction is not to use the words “clinically relevant”. This is confusing. Is it simply a distinction between including clinically relevant material but not calling something clinically relevant? Define clinically relevant and/or what it is not. In section 3.2 it lists “It may be appropriate to provide limited information relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified endpoints or clinical outcomes in the major trials and giving the main characteristics of the patient population.” It goes on to say “The term "statistically compelling" is a matter of assessment, often requiring specific case by case consideration. Its meaning within this document is further discussed in 6.4.1” which goes on to say “A compelling result is to be understood as a result that is seen as sufficiently "methodologically robust" to inform the prescriber and patient on the effect of the treatment in the authorised therapeutic indication” The terms “compelling” and “sufficiently methodologically robust” although seemingly clear could be interpretated differently. This is supported by the statement that the “term "statistically compelling" is a matter of assessment, often requiring specific case by case consideration”. To ensure consistency, at the time of this new guidance coming into effect, it would be helpful for the training material that accompany this role out to provide examples of what would and would not be considered “statistically compelling”. It is not clear how this would be managed in the ultra-rare space where the number of studies and sample sizes for studies would generally be smaller
9	EFPIA	**3.2 Scope of 5.1 (83-85)**: Remove word “exceptional”. “In cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations.”

10	EFPIA	**3.3 Structure of 5.1 (102-107)** : All paediatric data need to be reported in 5.1 (in label and off label). Please clarify where these data should go e.g. 'Clinical efficacy and safety' OR 'Paediatric population' (depending on in- or off-label)
11	EFPIA	**3.3 Scope of 5.1** (105): **Add** "Pharmacodynamic effects **(if known)"** or delete "(if known)" from MoA bullet.
12	EFPIA	**3.4 Target Audience (108-112)**: Consideration could be given to needs of other stakeholder functions assessment, e.g., HTA bodies in considering their requirements as a more holistic approach to the use of the document
13	EFPIA	**3.4 Target Audience (109 – 112)** The information on clinical efficacy will also be used in the discussion between the prescriber and the patient about treatment objectives and expected benefits. The SmPC will also be used by other stakeholders, e.g. As reference document for advertisement and reimbursement discussions. Reference to SmPC training document: https://www.ema.europa.eu/en/documents/presentation/presentation-introduction-summary-product-characteristics-guideline_en.pdf
14	EFPIA	**3.5 EPAR (120-123**): not all EPARs impacting section 5.1 are publicly available. How will this be addressed moving forward
15	EFPIA	**3.5 EPAR (120-123**): *"A link to the EPAR is foreseen in the SmPC Guideline. This link should be included in the SmPC to direct users to the availability of complementary and detailed scientific information and documentation of the decision-making process"*. This addition is encouraged but it is vital that any update to the QRD template is rolled in parallel with this update to this guide. It would also help prescribers if there was a hyperlink from the SmPC to the EPAR within the electronic version of the document, to help navigate to the correct document.
16	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (125-126 and 225)**: The general request for statistically compelling information appears to ignore the specific issues with small populations, pediatric subsets or rare diseases. Proposed change: "Results should ~~also~~ **generally** be statistically compelling. **In cases of a small population size, this will have to be a case-by-case decision."**
17	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (125-126)**: In order for the reader to understand and evaluate also the added value of a medicinal product in comparison to existing therapies, relevant comparative information may be of value to the prescriber and other HCPs, and may have to be included, provided it was robustly assessed in the clinical development program. This approach may also be supported by REGULATION (EU) 2021/2282. Proposed change:

		"Consideration may be given to relevant comparative information to understand the added value of a medicinal product, provided it was robustly assessed in the clinical development programme."
18	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (125-126)**: Key information for MAH to make claims must be maintained in Section 5.1 of SmPC as this reference document forms the basis of what can be claimed. If too brief with reference to details in EPAR which cannot be used for MAH claims, then makes it difficult for legitimate promotional activity. More clarity is needed on acceptable information regarding primary, secondary, exploratory, and QoL endpoints. Lines 130-131 explains what is not allowed, positive examples would also be useful for the language to use.
19	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (126)**: It states "The information should be statistically compelling" without mentioning clinical relevance, which is previously mentioned as important on lines 78 and 83. Suggest adding "clinical relevance" for consistency. Also, it would be helpful to add the reference of the section describing the meaning of "statistically compelling" as done on line 90.
20	EFPIA	**3.6 General Principles for the assessment of Section 5.1** (**127)** The exception for paediatrics is in line with line 76 that this may differ for paediatrics - suggest keeping original text but adding bracketed text: Proposed update: "Section 5.1 may provide further information on the authorised indication (e.g., clarification of what staging system for disease was used). There should be no recommendation for off-label use **(except for paediatrics).**
21	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (129)**: Remove the entire sentence or the word "recommended". **Consistency within a class and the therapeutic area should be considered.** Consistency. It should take precedence over conciseness to ensure parity between products
22	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (129)**: Is this principle applicable to ATMPs? In section 6.8, it mentions antibiotics and blood products.
23	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (129)**: For balance and additional context/consideration, a cross-reference should be made to section 6.8 of this Guideline where more detailed discussion is provided on this topic, including the need for product specific assessment.
24	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (130)**: More context should be included around the use or avoidance of the phrase "clinically relevant" as there will be instances where the clinical relevance of an observed effect is not completely or well understood, and this message will be important to convey to prescribers. For example, with vaccines a trend for slightly lower immunogenicity may be observed but the clinically relevance may be unknown because there is no correlate of protection.
25	EFPIA	**3.6 General Principles for the assessment of Section 5.1 (130):** While we understand that the aim of the SmPC is not to be promotional, the bullet point listed in line 130 "The promotional use of adjectives, adverbs should be avoided, e.g., very strong effect and high affinity…" may need be rephrased. In fact, adverbs such as "high" affinity if derived from established scientific sources can provide useful information to the prescriber to determine which product to

		use in overall context of a patient. For example, for certain antibody classes, the affinity is a mechanism that can distinguish between agonism/antagonism, or make an antibody better or worse. This text should also be aligned with line 190. Proposed update: "*The* ***~~promotional~~*** *use of adjectives, adverbs should be avoided, e.g., very strong effect and high affinity,* ***in absence of supporting scientific data****. Also, value statements like "clinically relevant" should be avoided* ***if not substantiated with clinical data***" **Information relating to time to onset of effect is permissible, where clinically important**."

(Add more rows as needed)

4. Mechanism of action

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	**(135)** General comment: in case of medicinal product indicated for use in combination with another medicine, shall the mechanism of action be described only for the main compound or is there an expectation to describe it also for the co-administered active substance? Could this be specified in this section?
2	EFPIA	**(142)**: Include a sentence related to MoA data generated and published for the same class of molecules (potentially even in a different indication). Information on the MoA can be included from published data of the same class of molecules even if in a different indication if it is reasonable that the mechanism of action will be identical. In case mechanistic clinical studies are available to further explain MOA, we propose that these are allowed to be included in section 5.1 to support the prescribers' decision to prescribe the product for an individual patient.
3	EFPIA	(139-142) Comment Translational data from relevant human cells are considered to be of high relevance and should be included. Proposed change: Important principles are:

		• Information in this section is usually based on in vitro and pre-clinical data, **including translational data using diseased human cells**, whereas the main clinical findings are presented with the results of the major clinical trials and are therefore out of scope of this subsection.
4	EFPIA	After line 153, please add another bullet point relevant for vaccines preventing infectious diseases, to appreciate the effect of vaccine on the population: **"-Information in this section may also relate to "burden of disease", based on epidemiology studies**.

(Add more rows as needed)

5. Pharmacodynamic effects

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	**(155)** The current guidance suggests that the Mode of Action section may already inform in general terms on the pharmacodynamic effects when describing the mechanism of action, and that the relevant favourable effects can be reflected as part of the main results of the clinical trial section. Considering this, the contents of this subsection on Pharmacodynamic effects could focus on other pharmacodynamic effects. This approach is supported. Considering the suggested approach for the section MoA and PD effect section, it is proposed to include additional pregiven subheaders into the Pharmacodynamic effects section of the SmPC guideline. This can guide the content covered in this section and thus will support constancy across different pharmaceuticals. **Proposal for potential subheadings could be:** **-Primary PD effects (if not reflected as part of the main results of the clinical trials), e.g., PD effects observed in exploratory study results.** **-Secondary PD effects, e.g., QT Prolongation or other safety issues**
2	EFPIA	**(155)** Please specify if this section can be removed completely if not relevant

3	EFPIA	**(156-166):** Nowhere in the document appears a request to either describe or demonstrate dose-response information which is "…important for safe and effective use of drugs in individual patients…" (CPMP/ICH/378/95) Proposed change: Before the sentence starting with "For anti-infectives,…" suggest to add (line 156): "**When demonstrated, a dose-response relationship on relevant pharmacodynamic endpoints is a strong element in support of efficacy or drug-related safety and could be described here" and/or in line 166 " Important pharmacodynamic effects observed in humans, based on convincing clinical data, e.g. demonstrating a dose-response relationship, and relevant for …"**
4	EFPIA	**(174-178)**: In some vaccine products (e.g., pandemic influenza vaccines) non-clinical efficacy data are included in section 5.1 (e.g., ferret challenge studies). Suggest to account for this possibility in the guidance.

(Add more rows as needed)

6. Clinical efficacy and safety

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	**6.1 General approach (183)**: Additional guidance regarding how best to summarise the main aspects of study design would be beneficial
2	EFPIA	**6.1 General approach (194-195):** We are supportive to keep EU CT number of clinical trials in the SmPC as unique identifier
3	EFPIA	**6.2 Patient characteristics (198-207)** • Inclusion of baseline COAs as important factors to describe the patient population. • There is mention of important aspects to include such as age and gender but there is no mention of race/ethnicity. Suggest including language on race/ethnicity being other important factors to include in patient population information. • As part of important subgroup suggest referring to the most vulnerable population as the age split (increasing age) and the frailty status in Older Adult population in line with EMA *Reflection paper on physical frailty: instruments*

		for baseline characterization of older populations in clinical trials. If efficacy is assessed in these subcategories, it should be included in the SmPC to guide prescriber's decision whether the benefit/risk of treatment is expected to be positive for a specific patient covered by the indication (**also applicable for Section 6.4.6, line 375-379).**
4	EFPIA	**6.3 Estimand (208-221)** • Suggest adding a clear definition of "endpoints", "point estimates" and "estimands" or add a reference to the relevant guidance providing a definition. • Estimands and treatment effects of interest are described in clinical protocols. These are aligned to trial objectives and form the basis of the trial design and the choice of estimands are discussed with regulators before trials begin. The estimands that are pre-specified in trial protocols should form the basis of the results that are shared in section 5.1 of the SmPC. Could you please be more specific about which information exactly needs to be included in relation to the estimand and whether a subsection on this topic is expected? • (212) Consider offering a suggestion instead of referring to 'estimand' e.g., add 'For example, refer to the treatment effect.
5	EFPIA	**6.3 Estimand (208-221):** This section does not seem to provide clear guidance on how/when to include estimands within section 5.1 but seems to focus more on which type of estimands are considered valuable (or not) for regulatory decision making. The comment on treatment policy estimands and alternative estimands seems more appropriate to a guideline focusing on protocol and clinical trial design than for SmPC drafting. In fact, the entire point of the estimand framework is to derive an estimand from the scientific objective of the trial. It is unclear why here a treatment policy is preferred a priori, without any reference to a scientific question. Sole recommendation of treatment policy strategy and comments on the hypothetical strategy contradict the ICH E9(R1) guidance and therapeutic guidelines (CPMP/EWP/1080/00). Prioritization of treatment policy strategy may not be aligned to the pre-specified design and analyses supporting approval. In several areas well-established endpoints use the composite strategy and not a treatment policy strategy (e.g. in the context of time-to-event and binary endpoints and the intercurrent event of death). Proposed change: **Remove lines 213-215 entirely**, given advice is provided in other therapeutic guidelines and prioritize alignment with the estimand used as a basis of approval.
6	EFPIA	**6.3 Estimand (216)**: The hypothetical estimand should not be considered to reflect an "Idealized situation." It often uses a model-based approach to estimate efficacy had the participant remained on treatment. It is ideal to assume all participants stayed on drug, but the estimates would generally be based on a model informed by the data, which could impute poor (non-ideal) responses based on the pattern of the data. Changing the handling strategy for an intercurrent event can be seen as a supplementary analysis for the primary estimand, as per ICH E9(R1) addendum, allowing for a

		comprehensive description of the effect of interest. It appears therefore odd that such supplementary analyses should be type I error protected. Also, Important additional information of relevance to the prescriber may be deemed important to include in exceptional situations, despite lack of inclusion in a formal testing strategy controlling for type I error. To make the statement that alternative estimand should have been pre-specified and include in exceptional situations, despite lack of inclusion in a formal testing strategy controlling for type I error-controlled testing hierarchy may restrict the flexibility to provide important additional information to the prescriber. There is also some contradiction with the statement made on lines 229-230. Proposed change: **Also remove lines 216-221 about the value of hypothetical estimands.**
7	EFPIA	**6.3 Estimand (216-221)** If EMA decides not to remove them, suggestion is made to re-write lines 216-221. • Consider reformulating *"regulatory experience with such estimands is limited"*. Analyses in the past often targeted hypothetical estimands by default due to the underlying assumptions of certain analysis models. Proposed change: **remove this part of the sentence and start with "There are still many concerns**… • **Rephrase** the considerations regarding discontinuation - the objective of this is not clear. Please clarify what is meant here (e.g., study treatment discontinuation or study discontinuation.) • The current language is too narrow: As acknowledged in EMA/CHMP/44762/2017, more complex methods beyond a 'type-1 error controlled testing hierarchy' exist to control type I error over both primary and secondary endpoints. Proposed change: **Replace 'type-1 error controlled testing hierarchy' by 'an adequate testing strategy controlling the overall Type I error rate'.** • Rather than refer to 'treatment policy estimands' and 'hypothetical estimands' clarify '**Estimands where treatment policy strategies are being used to address intercurrent events'** and **'Estimands where hypothetical strategies are being used to address intercurrent events'.** Estimands may use a mix of strategies to address intercurrent events, so it doesn't help to suggest an estimand always uses the same strategy to address all intercurrent events
8	EFPIA	**6.3 Estimand (213 – 221)** In this section it would be helpful to provide information about what is expected in the document with reference to clarification of the results and the estimands that they target. For example, in consideration that a treatment policy strategy has been applied for an important intercurrent event (for example use of a rescue therapy), such that the rescue therapy is considered part of the treatment strategies compared, it could be helpful to the prescriber to know how many participants in the study received rescue therapy on each treatment arm. If a hypothetical strategy is deemed appropriate, consider using terminology such that this can be identified. For example, using language

		similar to those used in the CHMP diabetes guideline, page 7, 'The treatment effect was estimated under the assumption that rescue medication…{…} was not introduced'. If a composite strategy has been applied for an intercurrent event, it could be helpful to the prescriber to know all the components of the endpoint and information about the breakdown of components (for example if use of rescue therapy were to indicate a lack of response). Proposed change: Consider providing guidance that would help the prescriber to understand the presented 'treatment effect' better. We suggest that the recommendation to report discontinuation be made more general to report the incidence of any relevant intercurrent event that could alter the interpretation of the result.
9	EFPIA	**6.3 Estimand (208-221)**: There is no specific instruction in this section on the issue of different estimands having different policies for the same endpoint. Suggest providing insight on use of different estimands for the same endpoint. For example, for a time to confirmed deterioration endpoint (TTCD), two different intercurrent events for a TTCD endpoint may result in the need for two different estimands. Suggest clarifying how this is managed.
10	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (224):** • *"Results presented should be (clinically) relevant to the prescriber*". Results should also be clinically relevant to the patients. • Does clinically relevant also mean clinically meaningful? Suggest definition of clinically relevant and add information on clinically meaningful to the section. • Worth including the sample size given this is included in the example. • It will be helpful to add any guidance related to whether the Sponsor should provide the most updated clinical efficacy data in the SmPC based on newer data cut, i.e., primary analysis vs. final analysis. Additional guidance on having the primary analysis in text (including the p-value) vs. final analysis in the table, etc., is also appreciated. This is to ensure consistency of data presentation in the SmPC across different products
11	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (226):** As per [1, p. 19], the SmPC is not directed to prescribers and patients, but to "prescribers and other health-care professionals". Proposed change: *"A compelling result is to be understood as a result that is seen as sufficiently "methodologically robust" to inform the prescriber and* ~~*patient*~~ **HCPs** *on the effect of the treatment in the authorised therapeutic indication."*
12	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (225-233):** The principles that results should be clinically relevant and statistically compelling is acknowledged and supported. However, the focus on Type I error control seems unnecessarily strict. While provisions are made for "other statistically compelling" data to be included, the wording and guidance appears quite limiting. While multiplicity control is considered important for regulatory filings, historically strict multiplicity control across (all) dose levels and endpoints has not been required in the EU. Provided that, for example, endpoints are clinically relevant and the risk of showing false positives can be excluded (e.g., highly significant results, consistency within/outside a trial etc.). Stating that this would only apply "exceptionally" does not appear appropriate.

		It is recommended to revise the wording to remove the "Exceptional" and state that "In appropriate situations…" Proposed change: ~~In exceptional cases~~ **Where appropriate,** several other important…
13	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (Lines 227 - 230, 249 – 251, 311 -320): Major Comment**: there is a lack of clarity within the guidance on whether secondary endpoints for which the type-1 error is controlled should or shouldn't be presented in an SmPC. In lines 247 -249, the guidance states *"inclusion of many secondary endpoints should be avoided. Even if type-1 error controlled and statistically significant, secondary endpoints are not necessarily of sufficient interest to the prescriber to warrant inclusion"* – leading the reader to conclude that a secondary endpoint included in the testing strategy and found to be statistically significant might not be included in the SmPC. However, lines 311-313 of the guidance state *"**the endpoints declared statistically significant in a confirmatory test** (usually, primary endpoints based on which conclusions were made) **should be highlighted** and declared as those for which a confirmatory conclusion on a positive treatment effect could be made"* (emphasis added) – and so the reader could reasonably conclude that a secondary endpoint included in the testing strategy (and which was found to be statistically significant) could be included in the SmPC. Similarly, the guidance advice in lines 227-230 "*Predefinition of the endpoint within a statistical testing procedure that controls the type 1 error and a statistically significant results… provides the strongest ... methodologic support for the inclusion of an endpoint in section 5.1"* would lead the reader to conclude that a secondary endpoint included in the testing strategy and found to be statistically significant should be included in section 5.1 of the SmPC. We recommend providing clarity on the points raised above.
14	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (230-233):** Listed reasons could be more comprehensive. Include additional reasons such as large magnitude of effect and when all plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect. These are recognized reasons to upgrade quality according to GRADE (Grading of Recommendations Assessment, Development and Evaluation). Consider consistency across totality of evidence to be another reason.
15	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (232):** External data is mentioned however no further information is provided: ..."consistency within the trial and with external data..." Please clarify what is meant by the term "external data" and how it may be used to support consistency.
16	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented** (233): There is mention of one important methodological aspect considered for the acceptability of the result includes "objectivity of an endpoint in relation to the trial design." It is unclear what is meant by objectivity of an endpoint. For example, does this mean an objective endpoint, such as a biomarker? If so, then this is problematic for certain COAs. Please clarify and provide an example of what is meant by "objectivity of an endpoint in relation to the trial design".
17	EFPIA	**6.4 Efficacy results 6.4.1 What should be presented and what may be presented (223-236)**

		Additional guidance on when to present data in text vs. tables vs. graphs and whether the same data may be presented in different formats would be beneficial.
18	EFPIA	**6.4 Efficacy results 6.4.2 Endpoints** (238-246): • The primary endpoint is just one attribute of the primary estimand. It is not clear why the guidance is going back to talk about the "primary endpoint". Rather use "primary estimand". • It should be allowed to present components of composite endpoints with no restrictions, since other stakeholders may need to make use of the individual components. • It could be helpful to a prescriber to have information related to the inclusion of an intercurrent events as part of composite endpoint. For example, if early treatment discontinuation counts as 'non-response' for the derivation of an endpoint. Proposed change (if any): To suggest additional wording such as… Consider whether intercurrent events incorporated into a composite endpoint would be important to describe for the prescriber to have full appreciation of the composite endpoint. • Sometimes safety endpoints (not primary nor key secondary) turn out to be evidence of treatment benefit (implied efficacy) as it reduces the occurrence of serious/severe AEs or disease outcome. Can such data be presented in more detail in section 5.1 as evidence of treatment benefit? • *"Results are distinctive"* and the final point stating that the secondary endpoint *"include[s] information that is not covered by the primary endpoint"* seem duplicative? Suggest removing one point or the other and elaborate as to how these two points are considered different
19	EFPIA	**6.4 Efficacy results 6.4.2 Endpoints (242-243 & 395)**: The consideration of PROs only appears to be too narrow. PROs may be included in an overarching section of Patient Experience Data (PED) which encompasses PROs and Patient Preference Information (PPI). There is an emphasis from IMI PREFER and EMA as to how PPI can support decision making and the benefit-risk assessment. Given the SmPC's objective is to support the prescriber's/HCP's decision whether the treatment is expected to be positive for a specific patient, PED/PROs/PPIs should be considered appropriate for inclusion into Section 5.1 of the SmPC and therefore guidance on what/how to include this information should be an integral part of the Guide to Assessors. See also "Patient experience data in EU medicines development and regulatory decision-making, EMA/786952/2022". Also, the EMA regulatory strategy to 2025 is supportive of Reinforce patient relevance in evidence generation. Proposed change: ***"Secondary endpoints [10] and Patient Experience Data (PED) [x] may be used to contextualise the effect on the primary endpoint in terms of clinical benefit, e.g., by complementing objective measurements by PROs PED reflecting the clinical impact."***
20	EFPIA	**6.4 Efficacy results 6.4.2 Endpoints** (245-246): Agree in principle that redundancy in endpoints should be avoided (i.e., additional endpoints should "include information that is not covered by the primary endpoint").

		• However, one point to keep in mind is that there are some composite endpoints that cover similar concepts, but that are preferentially used in one region versus the other. While the SmPC will focus on those endpoints that are more commonly used in EU, similar endpoints that are used in other regions may provide helpful insight. • *"This applies, e.g., to secondary endpoints that are expected to be highly correlated to another endpoint, present the same finding in different ways or to endpoints that are part of a causal chain from treatment to effect."*. We fully agree that a "finding" (which we interpret as 'drug effect ona concept of interest') should be presented only once. However, a high correlation between endpoints does not equate to assessing the same concept. Sometimes it is warranted to highlight multiple, related but different, concepts-of-interest in the causal chain from treatment to effect if these are central to the patient experience. We therefore suggest **removing the examples regarding "high correlation" and "causal chain" (lines 249-251) and focus on the repetition of a drug effect on the same, or substantially overlapping, concepts-of-interest (i.e. "same findings").** • Endpoints may change over time, and to allow interpretation of newer products vs. older products inclusion of older (similar endpoints) might be appropriate.Proposed change: "*… are robust.* ***However, as the use of endpoints within a disease area may change over time, secondary endpoints might be included to allow comparison with previously approved products"*** • Could it be clarified what is meant with "non-significant endpoints"? Would this refer to endpoints that do not reach statistical significance or to endpoints that are not statistically powered? Additionally, in the same section, we would like to request the Agency to elaborate more on the relevance (or lack of thereof) of exploratory endpoints. In the guide it is unclear if this type of analyses is covered under the "non-significant endpoints" paragraph within section 6.4.2. • In relation to orphan diseases, we assume that the rationale for including non-significant effects in primary endpoints will apply to all endpoints. Proposed change: *"… in the case of orphan diseases where (at the standard level), non- significant effects in* ***all*** ~~*primary*~~ *endpoints might be acceptable to support efficacy."* • **(259):** Add: "including exploratory endpoints". "Other endpoints (incl. exploratory endpoints) may additionally be suggested for inclusion by CHMP, if results are judged to be informative for the prescriber."
21	EFPIA	**6.4 Efficacy results 6.4.2 Endpoints (264-265):** Confusing statement about reporting negative results if CDP includes both positive and negative trials. Is this something new or has been done in the past? Clarify expectations around reporting negative results. Is it for failed endpoints in populations covered by the target population? In principle, target population should only reflect patients for each benefit/risk has been proven, supported by positive trials.
22	EFPIA	**6.4 Efficacy results 6.4.3 How to present (266-280):** • It is not clear how to determine if time-to-event endpoints is important other than if it has been tested and part of Type I error control. Proposed change: Clarify how one defines "most important" other than a time-to-event endpoint that has been included in testing hierarchy.

		• It is not clear how “non-negligible” discontinuation rates or important intercurrent events more generally would be defined (see also previous comment on how to present estimands). Proposed change: Broaden the scope from discontinuations to intercurrent events more generally and clarify in as general terms as possible what would meet the criteria of “non-negligible” treatment/study discontinuation rates or intercurrent event more generally. • Because presentation of multiple endpoints showing the same clinical effect gives reassurance to HCP on the clinical effect and totality of data, it may be appropriate in some circumstances to include “multiple endpoints”. We suggest a word “in general” is added, as shown in bold, to nuance the point on “redundancy”: *“Redundancy should **in general** be avoided in presenting the same information in text and tables or figures and as multiple endpoints that essentially show the same clinical effect”.* • *F*or the primary endpoint it might make sense to present the data both in text and tables. For the other agree, duplication should be avoided.
23	EFPIA	**6.4 Efficacy results 6.4.4 Alternative presentation of endpoints and alternative endpoints (282)** In addition to PRO’s describing the impact of the clinical (primary endpoint) they should also be considered when they are standardly used in clinical practice to manage patient care and/or inform shared decision making between the patient and clinician. Also in this section, the guidance suggests that multiple endpoints that may be highly correlated with the primary endpoint be avoided. An exception to include is PROs that assist a patient in understanding the relevance of the clinical endpoint from their perspective, such as trials with biomarkers as a primary endpoint.
24	EFPIA	**6.4 Efficacy results 6.4.4 Alternative presentation of endpoints and alternative endpoints (290-298):** The term MCID (=minimal important clinical difference) does not clarify if the threshold is for a cohort of patients or if it represents a meaningful difference on an individual level. Different methods (anchor-based, distribution based) may result in a potential range of thresholds that can be considered clinically relevant. It is uncertain if a minimal difference (MCID) impacts the majority of patients. The threshold should be based upon a “meaningful change” threshold with a sound scientific rationale. Proposed change: *“Formally defined endpoints can be complex and difficult to appreciate. In such cases, it is possible to complement the original endpoint with a related endpoint – e.g., complement a mean improvement on a Visual Analogue Scale (VAS) to the percentage of responders whose improvement exceeded ~~a minimal clinically important difference (MCID)~~ **meaningful** **within-patient change** on the same VAS in each treatment arm. Presentation of responder rates, using established ~~indisputable~~ **and justified** criteria, may give a flavour of how many patients experience a clinically relevant improvement (e.g., "40% of the subjects had a 50% reduction in monthly migraine days (baseline 8 days)".*
25	EFPIA	**6.4 Efficacy results 6.4.5 Confidence intervals and p-values (300-303)**: While we agree that confidence intervals are more informative, and p-values should be used judiciously in Section 5.1, we do think they are still of clinical interest (at least for the primary endpoint). We would recommend continuing include p-values in the text or tables as it clearly indicates which

		analysis has been multiplicity-controlled and reports the statistical significance per the prespecified SAP. Not including them for the graphs may be acceptable if they are in the text/tables. Reporting solely on the 95%CI is not recommended as it may lead to confusion, particularly with studies aimed at estimation purposes. Furthermore, CSR reported CIs are typically not adjusted for multiplicity. Confidence interval approach isn't necessarily equivalent to the statistical test results by p-value due to the multiple analyses procedure. This has also practical considerations considering the historical use of p-values, and their presence throughout product-information. The use of p-values throughout current product information vs. the new guidance will create a large discrepancy between older and newer products. It is not self-evident that this will improve the usability/readability of the SmPC. If p-value should be restricted to EPAR, does that mean in promotional material we can use the p-value as it is reflected in EMA approved document?.
26	EFPIA	**6.4 Efficacy results 6.4.5 Confidence intervals and p-values (314):** The text reads *"... the magnitude of the treatment effect is indeed also relevant from a clinical point of view."* Does this mean from the perspective of an HCP only or should it read "from a patient's point of view"? Clarification is needed on what is meant by "clinical point of view" - does this mean from a HCP's perspective?
27	EFPIA	**6.4 Efficacy results 6.4.5 Confidence intervals and p-values (316):** In Section 6.4.1 it says that usually 95% confidence intervals are sufficient. But here, adjusted confidence intervals are mentioned. Say what type of confidence intervals should be presented. We strongly favour to **always present 95% confidence intervals**, irrespective of the multiple testing strategy. Confidence intervals serve to quantify uncertainty in estimation of a population parameter and therefore a different purpose than, e.g., p-values. Hypothesis test decision must not be reproducible using confidence intervals. Reference to *"adjusted confidence intervals"* is unclear. It is well-known that methods for constructing adjusted confidence regions/intervals that provide a straightforward interpretation are not be available even for a simple hierarchical test procedure, even less so for more complex multiple test procedures. These complex procedures do have a strong control of the overall Type I error rate but methods for constructing multidimensional confidence regions might not be available. EMA could provide further clarification in terms of selection of complex multiplicity adjustment procedures/methods. For example, would it be acceptable to suggest that unadjusted confidence intervals (and p-values) should also be presented as supplementary descriptive information regardless of the multiplicity procedure? This is particularly relevant in the situation where meaningful confidence regions corresponding to the multiplicity procedure do not exist as overly conservative intervals may not be very informative.
28	EFPIA	**6.4 Efficacy results 6.4.5 Confidence intervals and p-values (325-329):** When referring to an updated or final analysis, it should be made clear that this represents an addition to the Efficacy Results presented in Section 5.1 by the MAH as part of a later, separate update from the original application (often several years later). Suggest adding a sentence to clarify that updates and/or a final analysis represent a separate update later than the original Section 5.1 at the time of approval.

29	EFPIA	**6.4 Efficacy results 6.4.5 Confidence intervals and p-values (327-329)**: To improve readability, it would be recommended to include all endpoints into a tabular format. Proposed change: ~~*Therefore, it should be made clear that this in-text presentation of those endpoints reflects the confirmatory level of evidence concluded from the trial whereas the tables may include updated data*~~. ***The results of the inferential analyses should be presented in a clear table; the type of endpoint (confirmatory /multiplicity controlled vs. others) could be clarified in footnotes.***
30	EFPIA	**6.4 Efficacy results 6.4.6 Subgroup analyses, exploratory analyses and post-hoc analyses (345)**. **Major Comment:** Referring to section 6.4.6, we would like to debate the appropriateness of including efficacy-related information in section 4.4 of the EU SmPC. We are of the opinion that information on uncertainties or difference in treatment effects that do not pose a risk to the patient should be emphasized in section 5.1 and not section 4.4. Subgroup analyses are usually not powered and often do not include enough patient numbers to draw a statistically solid conclusion. Therefore, a level of uncertainty will always remain. We are therefore of the opinion that inclusion of such information in section 4.4. could lead to the inclusion of irrelevant information within this section and/or of repetition of information from section 5.1. Inclusion of this information solely in section 5.1 will provide a consolidated place where the information can be found by the prescriber and allow to put such information into the context of the overall data and patient population enrolled in the clinical study. Proposed change: If the Agency still prefers to include efficacy information in section 4.4, we recommend to clarify that only information pertaining to populations that might experience a higher risk should be included.
31	EFPIA	**6.4 Efficacy results 6.4.6 Subgroup analyses, exploratory analyses and post-hoc analyses (352-353):** Suggest including section 4.2 in this list of other sections. Rationale: Section 4.2 can include dosing/posology for special populations. Proposed changes to text (shown in track changes): … Where a subgroup finding that is found to be credible indicates that therapeutic efficacy or positive benefit/risk is not established, or indeed that benefit/risk is negative, it should be reflected in section 4.1**, 4.2**, 4.3 or 4.4 of the SmPC, as appropriate. [11, p. 20]
32	EFPIA	**6.4 Efficacy results 6.4.6 Subgroup analyses, exploratory analyses and post-hoc analyses (382-386)** Guidance on what information to include in case the indication/target population is restricted to a subgroup of a trial population is appreciated. The recommendation to include the main results of the inferential analysis of the study in text and that the results in the authorised indication/population should be presented in tables and graphs, does not appear to be self-evident and might be easily misunderstood. Also, it should be considered that most often multiplicity control would be based on the full population. Proposed change

		In case the indication/target population is restricted to a subgroup of a trial population, ~~the main~~ ***relevant*** *results of the inferential analysis of the study should be presented in ~~text~~* ***tabulated format with clear titles / table descriptions clarifying the appropriate populations****, despite fact …*
33	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (395):** This section only details PROs but it does not mention other types of COAs such as Clinician-reported, performance reported, or observer reported outcome assessments. The latter is especially important for indications whereby the individual does not have optimal insight to report for themselves, such as children or people with dementia. Suggest commenting and covering other types of COAs including PROs. Suggestion is made for an explicit mention in SmPC Section 5.1 of Patient Experience Data (PED), including PROs and also Patient preference studies.
34	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (396)**: Recognition that PROs are not different from other endpoints is welcomed. Yet later discounts PROs in an open label design. This suggests that they are being treated differently. When PROs are efficacy endpoints, the contents included in the subsections within Section 6.4 may be relevant to PROs. In addition, Section 6.4.5 (line 300) states that *"Confidence intervals are considered more informative to the prescriber than p-values, which are difficult to interpret. Therefore, the presentation of confidence intervals is strongly preferred over the presentation of p-values ...".* But PROs are not exclusively used to compare treatment effects in terms of superior benefits. They also provide complementary information about the tolerability of a drug. Such information may support the physician in the assessment of the benefit-risk for the individual patient and in the dialogue with the patient. Proposed change The assessment of PROs is not different from other endpoints ~~in the general case~~ **and are, in many cases, used as efficacy endpoints. PRO claims should be based on design and analysis plans that are statistically and methodologically rigorous. Like any other endpoint (as described in section 6.4.5) it is recommended to apply confidence intervals, which may be more informative than p-values.** PRO claims **for benefit** should be based on type 1 error-controlled analyses. **However, PROs could also inform about the tolerability of the drug (e.g., PRO CTCAE instrument).**
35	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (398-399)**: Quality of life (QoL) and health-related quality of life (HRQoL) are used in Section 6.4.8. There are differences between QoL and HRQoL. In pharmaceutical clinical trials, the focus is almost exclusively on HRQoL. It is recommended that consistent reference to HRQoL be used throughout the document. In addition to HRQoL assessment, in-trial qualitative interviews conducted to quantify the patient experience and meaningful change in disease related symptoms are also clinically relevant to the prescriber. Proposed change This also applies to **Health-Related** Quality of Life assessments **as well as in-trial qualitative interviews to quantify the patient experience and meaningful change in disease related symptoms** ~~a subtype of PROs~~.

36	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (399-400)**: We request to include additional detail for the reviewer on what is to be considered “clinically relevant”. Outcomes assessed by patients are consider relevant to patient and for treatment of the disease.
37	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (400-402)**: The term MCID (=minimal important clinical difference) does not clarify if the threshold is for a cohort of patients or if it represents a meaningful difference on an individual level. It is uncertain if a minimal difference impacts the majority of patients. Thresholds my depend on the method employed. Thus, a sound scientific justification should be provided for the “meaningful within-patient change” or “meaningful within-group change”. Proposed change: To establish clinical relevance, the effect size should exceed the **pre-defined and scientifically justified meaningful change (within patient and/or within group)**. ~~'minimal clinically important difference', which should in itself be well- justified on a clinical basis a priori.~~
38	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (403)**: A comment on PROs needing to be adequately validated is mentioned with no explanation on what is meant by this term. Please explain what is considered 'validated' and/or provide a reference detailing what EMA looks for in terms of a 'validated' measure. The document states that "PRO instruments should be adequately validated." Validation is a broad topic and there are different approaches to validation (i.e., different criteria for demonstrating validity of a PRO instrument). For instance, in the FDA patient-focused drug development (PFDD) draft guidance 3 - Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments and draft Guidance 4 - Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making, the modern view of validity was recommended and referenced. It is recommended that the concept of "adequate validation" is defined. This would provide clarity to sponsors as they conduct validation work. Literature references on validation, reflecting EMA's recommended approach to/criteria for validation, should also be included. For example: 1. American Educational Research Association, American Psychological Association, Joint Committee on Standards for Educational and Psychological Testing (U.S.), & National Council on Measurement in Education (2014). Standards for educational and psychological testing. Washington, DC: American Educational Research Association. 2. Kane, M. T. (2013). Validating the interpretations and uses of test scores. Journal of Educational Measurement, 50, 1–73. 3. Messick, S. (1989). Validity. In R. L. Linn (Ed.), Educational measurement (3rd ed., pp. 13–103). New York: American Council on

		Education and Macmillan. 4. Sawatzky R, Chan EKH, Zumbo BD, Ahmed S, Bartlett SJ, Bingham III CO, Gardner W, Jutai J, Kuspinar A, Sajobi T, Lix LM. Montreal Accord on Patient-Reported Outcomes (PROs) use series–Paper 7: modern perspectives of measurement validation emphasize justification of inferences based on patient reported outcome scores. Journal of Clinical Epidemiology. 2017 Sep 1;89:154-9. 5. Weinfurt KP. Constructing arguments for the interpretation and use of patient-reported outcome measures in research: an application of modern validity theory. Quality of Life Research. 2021 Jun;30(6):1715-22.
39	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (403-404):** There appears to be inconsistency in the terms used here (i.e., instruments, scale). Consistency should be applied, and clarification made. Since questionnaires composed of scales are validated at the scale level, use of the scale should maintain its validation when used as part of an item library.
40	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (403-404):** We see no rational to include the statement that "*PRO data are often not considered appropriate for the SmPC section 5.1.",* since PED, including but not limited to PRO, are increasingly being part of benefit/risk assessment and results should inform prescriber's decision to the extension they inform regulators. Current statement inherently runs counter to the opening sentence that they are not different from other endpoints and seems to effectively discourage the use of PROs and inclusion into the SmPC, what contrasts with wording in the " Guideline on the clinical evaluation of anticancer medicinal products EMA/CHMP/205/95 Rev.6", Section 7.1.6, page 24. which is strongly supportive of PROs. Furthermore, it does not fully address EMAs position on patient-focused medicines development. The argumentation for this premise (lines 405-407) seems comparable to EMAs 2005 reflection paper on the use of health-related quality of life measures in the evaluation of medicinal products, but it should be considered that the procedures around-, and science of PED data collection and analysis have evolved tremendously in the past two decades. Specifically, due to the evolution in the field, the amount of missing PRO data has decreased, and determining "clinical" relevance is a main aspect in the PRO development and validation. As for the mentioned potential biases and multiplicity considerations (lines 406-407), these are important to consider, but they are not specific to PROs, and may relate to any study endpoint (albeit in varying degrees). Patient experience data is important to clinicians when discussing benefits and risks of medicines with their patients. Given the importance of describing robust PED results for prescribers and patients, there could be benefit in starting the paragraph with the positive position of explaining when it may be appropriate to present the results from a PRO.

		We do agree that the general requirements for inclusion apply, and that the PED data should be scientifically sound. Missingness, potential bias due to an open-label study design or unblinding by toxicity, multiplicity issues could also be relevant for other endpoints, e.g., investigator assessments of tumor response or disease control. Multiplicity issues may concern analyses at different time, endpoints, subgroup analyses, secondary endpoints for efficacy and also when safety endpoints are statistically compared. The extent of bias due to open-label study designs does not exclusively affect PRO endpoints. In fact, the phrase that PROs aren't appropriate because of potential bias due to an open-label study design is not supported by evidence. The literature does not support this statement. The validity of PRO results from open label RCTs have been repeatedly demonstrated. Efficace et al. (2022) did not observe statistically significant association between treatment concealment (blinded vs open label) with the proportion of trials favoring the experimental treatment. Furthermore, it has been shown that patients do not change their responses to PROs regardless of a blinded or unblinded clinical trial (Atkinson et al. 2017). References: Efficace, Fabio, David Cella, Neil K. Aaronson, Melanie Calvert, Francesco Cottone, Massimo Di Maio, Francesco Perrone et al. "Impact of blinding on patient-reported outcome differences between treatment arms in cancer randomized controlled trials." JNCI: Journal of the National Cancer Institute 114, no. 3 (2022): 471-474.Atkinson, Thomas M., Jan-Samuel Wagner, and Ethan Basch. "Trustworthiness of patient-reported outcomes in unblinded cancer clinical trials." JAMA oncology 3, no. 6 (2017): 738-739 To note also that current wording leaves scope for different interpretation across. There is an identified risk of inconsistency across assessors, across products within a class/indication. EMA should implement an approach that drives consistency. Proposed change: ~~*PRO data are often not considered appropriate for the SmPC section 5.1. This may be because of extensive missing data,potential bias due to an open-label study design or unblinding by toxicity, the multiplicity of Quality of Life assessments,and uncertain clinical relevance*~~*. PED data might be appropriate for the SmPC section 5.1. If clinically relevant , statistically robust, and/**or** informative, the results can be reflected in 5.1, ~~and~~ **if** no other sections of the SmPC are appropriate*.

41	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (407-408):** The previous statement about open label would seem to discount the statement “If clinically relevant, statistically robust, and informative, the results can be reflected in 5.1, and no other sections of the SmPC are appropriate.” How are tolerability endpoints which are also beneficial in prescribing going to be included?
42	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (405)**: Although there is specific guidance on PRO data in the context of oncology studies (i.e., Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man – the use of patient-reported outcome (PRO) measures in oncology studies – Scientific guideline l European Medicines Agency (europa.eu)), there is no general guidance on considerations for inclusion of PRO in the SmPC or specific guidance on this topic in therapeutic areas beyond oncology. Such guidance would help developers better understand expectations for appropriateness of clinically relevant PRO data for inclusion in SmPC.
43	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (410)**: We would welcome additional clarifications on and be specific about what "overlapping" means.
44	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (410-413)**: It is requested to provide rationale on how the “most representative PRO(s)” is to be selected for inclusion in the SmPC
45	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (410)**: We recognize the importance of careful selection of clinical data to be conveyed in the SmPC and applaud the parsimonious approach proposed to ensure control of type I error (true of all types of endpoints and not specific to PROs as suggested in line 410). However, we also believe that patients living with serious and/or chronic conditions with diverse presentation, multifactorial treatment considerations, and varying levels of severity need to be informed about the treatment effect on all core disease aspects.
46	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (414):** We request EMA clarify what is meant by “unfamiliar” in the sentence “If it is considered important to include an unfamiliar PRO…”

47	EFPIA	**6.4 Efficacy results 6.4.8 Patient-reported outcomes (PROs) (414-416)** : It is recommended that presentation of mean treatment effect (or responder analysis or time-to-event analysis, if appropriate) be included if the unfamiliar/new PRO measure possesses adequate evidence to support its reliability and validity. Proposed change If it is considered important to include an unfamiliar PRO in 5.1, it may be considered to present the data **either** as a responder fraction **and/**or a time-to-event measure ~~rather than~~ **and/or, where adequate evidence to support reliability and validity is available**, ~~as a~~ mean treatment effect [→6.4.4].
48	EFPIA	**6.4 Efficacy results 6.4.9 Graphs (418):** • It would be helpful to understand guidance on 1) the presentation of results over time which go beyond the primary endpoint (e.g., showing data to 1- year for a study with a primary endpoint at Week 16), and 2) presentation of data during study periods without a control (either placebo or active comparator. • Lines 432-435: in the case of dual primary endpoints or key secondary endpoints it is appropriate and informative to include more than one graph per indication. • Lines 442-443: Waterfall plots can still provide relevant information to prescribers in case of single arm trial.
49	EFPIA	**6.4 Efficacy results 6.4.9 Graphs (434-435):** This statement could be interpreted as if OS is always more relevant than PFS. In a number of cases OS in oncology trials is not interpretable/relevant even if mature data exist (e.g. when patients are allowed to switch to the investigational treatment after progression). Proposed change: Remove example of OS/PFS K-M curves and replace with generic statement to include most relevant graph.
50	EFPIA	**6.4 Efficacy results 6.4.9 Graphs (436-438)** It seems contradictory to state that only reasonably mature K-M curves should be presented in the SmPC but to then go on to state that they may be required as a precautionary measure. It may be clearer/less contradictory to reverse the order of these statement.

51	EFPIA	**6.4 Efficacy results 6.4.9 Graphs (438)** If OS curves cannot be included initially (because of lack of maturity) there should be support for including such curves once more mature data becomes available. It is therefore recommended that guidance be provided on when updated OS curves can be included. Proposed change ... may be required. **If more mature OS curves become available in later analyses these could be included into the SmPC as part of a labelling update.**
52	EFPIA	**6.4 Efficacy results 6.4.10 Single-arm trials (446-447):** • Largely the same principles apply as for Randomised Clinical Trials, but the focus will be on endpoints that isolate a direct drug effect, such as objective response rates (ORR). Can there be clarification on the inclusion of tolerability endpoints that also would focus on the drug effect? • Clarification of the term 'Objective Response Rate' would be helpful as only used in the oncology disease area.
53	EFPIA	**6.4 Efficacy results 6.4.10 Single-arm trials (448-451)**: Major Comment: We would like for EMA to reconsider the statement on SAT, for which OS and PFS in oncology are not suitable for section 5.1. OS and PFS can still be presented objectively in section 5.1 and still provide useful information to the prescriber, especially when treatment effect is considered large or when no alternative therapies are available. As stated in the reflection paper on SATs (EMA/CHMP/564424/2021) the concept of "treatment effect" is a theoretical concept which requires detailed knowledge of the clinical context. Therefore, we are of the opinion that inclusion of OS and PFS information should be evaluated on a case-by-case scenario, based on the data presented and on the clinical context. Proposed change (if any): Remove direct reference to PFS and OS in oncology. Keep only a general statement on isolation of drug effect. Alternatively, refer to PFS and OS mentioning that these will be evaluated on a case-by-case scenario.
54	EFPIA	**6.4 Efficacy results 6.4.10 Single-arm trials (448-451):** The statement *"The presentation of comparisons of SAT data to an external or historical control groups is generally not appropriate due to deficient control of potential bias"* is not supported

		(See also comments on Section 6.15.2). The “Guideline on the clinical evaluation of anticancer medicinal products - EMA/CHMP/205/95 Rev.6" provides important considerations on how to ensure that external controls are valid. If such steps are taken inclusion of relevant data in section 5.1 could be suitable. Particularly in rare populations where RCTs are not feasible and SATs are conducted, there is value in providing HCPs with information from external and historical control groups for contextualization of the treatment effect seen in the SAT. If a comparison to historical control or other external control information has been fully justified and is part of the totality of evidence leading to an approval, it could be deemed appropriate to provide this information to the prescriber to put the results of a single arm trial into context, in absence of a comparator arm. While it is understood that the bar for inclusion of external data might be high, more flexibility should be introduced and guidance on when external data might be included should be provided. Given the increased acceptability of the use of real-world evidence by EMA to inform regulatory decision making throughout the product life cycle, it is important to ensure that the guidance on Section 5.1 of the SmPC be future proof. Proposed text: The presentation of comparisons of SAT data to an external or historical control groups ~~is generally not appropriate~~ **should be appropriately justified, to including demonstrating mitigation of** ~~due to deficient control of~~ potential bias. [→6.15.2 Additionally, the guide discusses external/historical controls within the context of SATs only. Make external/historical comparisons its own section. There could be reasons to consider reporting this, even for RCTs or observational trials. The guide could provide the guidance on what to consider when adjudicating these decisions.
55	EFPIA	**6.5 Safety results (460):** • Typically, clinical trial study design and endpoint objectives are described in Section 5.1 as they precede efficacy results that follow. However, in cases where a clinical trial does not inform efficacy but is a key source of information for other important topics for the medicinal product (i.e., safety and/or PK), guidance on the appropriate section to provide a such study description could be provided. For example, if the primary aim of a study is PK-related, should the study description reside in Section 5.2 or should it reside in Section 5.1 if it also contributes to clinical safety information? It is acknowledged that not every single clinical trial scenario can be covered, but guiding principles on deciding the appropriate primary section to capture study descriptions could be helpful. • There is no mention of tolerability assessments. It would be helpful to see something on how to include these.

		• Unclear what "clinical relevance" and "statistical robustness" means for safety. Typically, when pre-specified endpoints are defined in safety, they are clinically relevant and are an important part of the benefit-risk evaluation. Also, studies are typically not powered to detect a difference. Proposed change: Clarify that clinical relevance is implied for all pre-specified safety endpoints (and composite of multiple terms). Please remove the reference to "statistical robustness".
56	EFPIA	**6.6 Paediatrics (471):** • There is no mention of COAs. Clarify that this also applies to COAs. • *"... and efficacy should be described in 5.1 (independent of whether an indication is authorised".* All paediatric data need to be reported in 5.1 (in label and off label). Please clarify where these paediatric data should go e.g. 'Clinical efficacy and safety' OR 'Paediatric population' (depending on in- or off-label)
57	EFPIA	**6.7 Diagnostics. 6.7.1 (companion) diagnostic tests in the SmPC of a therapeutic agent (498-503)**: While guidance on diagnostics is appreciated, in some therapeutic areas (e.g., lung cancer) multiple established diagnostic tests will be used therefore it would be not possible to include all available diagnostic tests suitable for identification of patients. Proposed change The test employed in a trial should be included by brand name in 5.1 together with the population description of the trial, **as appropriate. In therapeutic areas where diagnostic tests are routinely used in clinical practice, specific tests are not required to be included in the SmPC.**
58	EFPIA	**6.10 Hybrid application (529)**: On section 6.10 Hybrid application, it is written that if the new hybrid follows the Reference Medicinal Product (RMP) for indication, route of administration and strength, then section 5.1 for Hybrid should be the same as for RMP. The proposed text appears too restrictive as sometimes pivotal efficacy/safety studies with the hybrid DP might be required even in case of same indication / same route / same strength (it was the case for extended-release oral products developed as need to define new dosing regimen).

		Proposed update: "*Section 5.1 content for a hybrid with a bridge to clinical data primarily* ***should*** *follow~~s~~ the reference medicinal product if the indications, route of administration, and strengths do not differ* ***and if no pivotal studies were conducted with the hybrid****.* *In other words, the information from the reference product's SmPC that applies to the hybrid (as evidenced by bridging to clinical data)* ***should generally*** *be included in 5.1 of the* ***hybrid unless exception when additional studies are performed****.*
59	EFPIA	**6.11 Biosimilars (539):** Include "covered by regulatory data protection": *"(except for indications or dosage forms still covered by patent law or regulatory data protection)"*
60	EFPIA	**6.12 Immunogenicity (549)**: Considering that Annex on SPC requirements to the "Guideline on Clinical Evaluation of New Vaccines" EMEA/CHMP/VWP/382702/2006 was superseded by the revised version of this Guideline (EMEA/CHMP/VWP/164653/05 Rev. 1) that does not include such an Annex, the paragraph on Section 5.1 from the "old" Annex on SPC requirements could be brought under immunogenicity here as it was considered helpful. The paragraph states: "This section should briefly summarise (tabulation may be appropriate) the most pertinent immunological data (using the most relevant parameters) and any estimates of efficacy or effectiveness considered to be valid (with caveats regarding the population in which these were measured). As necessary, the data should be broken down by primary series and boosting, by age group or by other factors, such as immunosuppression.The section may include details of the established or putative immunological correlate of protection."
61	EFPIA	**6.12 Immunogenicity (550-552):** Please add the following statement, as indicated in bold, to link observational studies for vaccines with the requirements for "observational studies" under section 6.15 (line 580): "*Observational data could be accepted for vaccines into SmPC 5.1. on a case-by- case basis, when considered the most relevant information to the prescriber and to other HCP or patients.* ***In line with section 6.15, observational data should be robust enough to be included".***
62	EFPIA	**6.13 Extrapolation (559-572)**: It is understood and acknowledged that details of extrapolation and its justification should be in the EPAR and that detailed outcomes of such studies do not need to be included in the SmPC.

		However, there should be appropriate latitude to allow (limited) information on these studies, used for extrapolation, to be included in the label where they are relevant to prescribers. This should not be limited just to *"data supporting the existing route of administration may be included in 5.1 if the information supports efficacy and safety of the new route of administration"* but may also support e.g. (just) the new route of administration and might have to include (high level) information on both the "old" (e.g., IV) and "new (e.g., SC) formulation. Note this may also include data from non-approved indications (see also comments on section 6.1 and 6.4) Ensure appropriate provisions are included for studies where data is extrapolated from non-approved indications and/or posology's - clarifying where such data can be included and at what level of detail. Proposed change *If a new route of administration (e.g., SC after original IV) is authorised for a product, ~~data supporting the existing route of administration may be included in 5.1~~* ***appropriate*** *~~if the~~ information ~~supports~~* ***supporting*** *efficacy and safety of the new route of administration,* ***should be included (including data on the original route of administration or even when the study is performed outside of the approved indications).***
63	EFPIA	**6.13 Extrapolation (560)**: Similarly to the comment for the Subgroup analyses section 6.4.6 above, we have concerns about the appropriateness of the inclusion of efficacy data within section 4.4. Proposed change: As above for section 6.4.6.
64	EFPIA	**6.14 Interim analysis and updated data (574)**: We would like for EMA to clarify whether information from the interim analysis can be maintained within the text (but removed from tables and replaced by the new data) similarly to the example provided at the end of this guideline. The wording included in section 6.14 may be interpreted that any data pertaining to the interim analysis should be removed from section 5.1. We would advise against such interpretation as interim analysis still provides information on benefit within the short term, which depending on the clinical context can still be considered beneficial to the patient.
65	EFPIA	**6.14 Interim analysis and updated data (576)**: "Adjusted confidence intervals": Adjusted for what? For early stopping of the trial?

66	EFPIA	**6.14 Interim analysis and updated data (576-579)** When the results of the interim data are the final analysis for the confirmatory endpoint demonstrating the positive impact of the drug/vaccine over of period of time, supporting by itself prescriber's decision whether the benefit/risk of treatment is expected, it is recommended to maintain that interim data (ground for MAA) and to complement them with End of Study data (that may be considered as additional/supportive information)
67	EFPIA	**6.15 Observational Studies (580-590):** The paragraph seems to convey the message that RWE is not accepted for inclusion in the SmPC for the recommended use, regardless of what the body evidence is. While the limitations of observational studies are acknowledged, we are of the opinion that it is still feasible to express uncertainties and highlight potential biases in a concise manner within section 5.1. Overall, we don't agree that observational information should be confined to the EPAR. Proposed change: ~~Currently, there is no agreed methodologically robust regulatory framework for the assessment of such as efficacy information As with all observational data, data quality and suitability for the SmPC remain the key concerns. The methodological and statistical concerns, such as the aspect of "(lack of) predefinition" and data-driven analysis, have not been solved convincingly, and bias (primarily confounding by indication) cannot be excluded. Therefore, observational data are usually not considered statistically robust to be included in the SmPC~~. **Observational data can be considered to be included in the SmPC upon discussion with CHMP on a case by case basis given that these methodological and statistical concerns are addressed** .
68	EFPIA	**6.15 Observational studies (580)** Additional details (or examples) of when observational data related to immunogenicity may be acceptable in section 5.1 would be helpful. Since in section 6.15.1 it is stated that there is no agreed methodological regulatory framework for the assessment of such efficacy information, it would be helpful to provide more guidance on this topic in the context of products based on immunogenicity data (e.g., vaccines).
69	EFPIA	**6.15 Observational studies (588):** Please paraphrase the term "confounding by indication", as it may not be well-known and is used ambiguously in the epidemiologic literature.
70	EFPIA	The draft guide mentions 3 main reasons for excluding external control data in the SmPC in order to provide context. In our opinion, it is possible to address these listed concerns that are not unique to external control arms

		• The same could apply to certain clinical designs, which may be difficult to interpret. Also, we believe that it is possible to include information from external controls in a concise way, while being clear about the possible differences in origin and methodology. • Comparator data from trials is included in a label. is not unique to external control data as comparator information is also presented for RCT trials. • New data with the same product also could arise from new trials and updates of observational data can follow the same process as for RCT. As for other data, it should be a case-by case-decision depending on the situation whether the use of external control data is allowed. Proposed change : ~~Potentially biased observational data should not be included in the SmPC~~, **External control data could be included in the SmPC on a case by case basis.** Hence, **respective lines 593 – 603 (starting from "Noting that it should not prevent the presentation of results of a SAT…." to "……are presented by a competitor)" are proposed to be deleted.**

(Add more rows as needed)

7. Example

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	It is appreciated that an example is given, but more are welcome: • Examples beyond OS (i.e. COA), • Examples on PRO &SAT as possible scenarios, • Example(s) of appropriate graphs (e.g., those not considered to include "overly fancy formatting) • Examples on special situations (e.g., extrapolation, graphs, tables, etc)

2	EFPIA	**Major Comment:** this example is inconsistent with the advice provided earlier in the guidance. We welcome the use of an example within the guidance and would strongly suggest that such an example should be consistent with the advice provided earlier about providing information on differences between treatment arms and presenting ratios together with corresponding absolute values. Specifically, the guidance states (lines 267 – 268) that "emphasis is on the treatment effects exerted by a produce, i.e., differences between treatment arms in controlled trials" and (lines 273 – 275) "Ratios (odds ratio, relative risk ratio, hazard ratio) and/or relative effects (relative risk reduction, percentage change) should be presented together with corresponding absolute values to help the reader to interpret the results in terms of clinical relevance" (emphasis added). However, the example in section 7 omits the differences between treatment arms for both the 'overall survival' and 'confirmed objectives response' endpoints and presents a ratio for the 'overall survival' endpoint (namely the hazard ratio) without the corresponding absolute difference.
3	EFPIA	Based on the example provided in the guideline, EMA is suggesting shifting forward a very statistically heavy format and text. We are wondering if such text would become too heavy for a prescriber, who may not be familiar with such level of statistical details. We are wondering whether such verbiage, such as reference to type I error control, would be more appropriate for the EPAR instead. We are strongly in favour of providing factual and statistically solid information and analyses for section 5.1, but we would recommend a focus toward the clinical context and clinical meaningfulness of the data than toward reaching 100% statistical focus/accuracy. We would also like to bring to EMA's attention that this example does not follow the recommendation provided within this guidance to limit the description of the statistical model to the footnotes of tables.
4	EFPIA	A clearer distinction should be made between Guideline text and mock-up SmPC text for illustrative purposes
5	EFPIA	The term 'studywise error rate' is not a well-established term (e.g., what is meant by 'study'?). Proposed change: Please provide a definition or use an alternative term such as 'overall type I error rate.

(Add more rows as needed)