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Committee for Medicinal Products for Human Use (CHMP)

# Assessment of SmPC section 5.1

## A Guide for Assessors of Centralised Applications

## Draft

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**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
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# Table of Contents

# 1 Abbreviations

| | |
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| CHMP | committee for human medicinal products |
| EPAR | European public assessment report |
| HCP | health care professional |
| HRQoL | health-related quality of life |
| HTA | healthcare technology assessment (body) |
| K-M | Kaplan-Meier |
| MAH | marketing authorisation holder |
| MCID | minimal clinically important difference |
| NCA | national competent authority |
| ORR | objective response rate |
| PIL | patient information leaflet |
| PRO | patient-reported outcome |
| SAT | single-arm trial |
| SAWP | scientific advice working party |
| SmPC | summary of product characteristics |
| VAS | visual analogue scale |

# 2 Introduction

## *2.1 Problem statement*

CHMP has frequent discussions on SmPC section 5.1, e.g., concerning what information to include in 5.1.

The SmPC is a key information source for prescribers. HCPs and patients ask that the regulatory information be optimised to facilitate use and aid therapeutic choice at an individual level. However, too much text is contrary to the principles of brevity and conciseness recommended in the EC SmPC Guideline in agreement with the CHMP. [1, pp. 19–20]

## *2.2 Objective*

This document is written as a guide to assessors of the SmPC in centralised procedures. Moreover, applicants and MAHs are expected to consider this document when preparing an SmPC for review, e.g., in the context of a marketing authorisation application or an extension of indication.

This document should be considered together with other CHMP initiatives and guidance on benefit/risk evaluation, subgroups analyses, extrapolation, and[2] therapeutic class specific considerations. [2] The exact content of this section 5.1 remains a case-by-case decision.

# 3 Principles of the regulatory framework of 5.1

## *3.1 What is it for?*

The SmPC is a legal document that defines the conditions of use under which benefit/risk balance has been considered positive, [→3.6][3] **The SmPC is the basis of information for HCPs on how to use the medicine safely and effectively**[1, p. 2]. It is also the reference document to be used for any advertisement related to the product [3, Art 87]. The objective of the information in 5.1 is to support the prescriber's decision whether the benefit/risk of treatment is expected to be positive for a specific patient covered by the indication statement by presenting the main efficacy results as concise, reliable and ready to use information [4]. Section 5.1 does not provide the grounds for the committee opinion on whether or not to approve an application, this is discussed in the EPAR [→3.5].

## *3.2 Scope of 5.1*

Section 5.1 should be limited to the indication, target population and posology that are authorised. No information should be given on indications /populations that were not applied for or were rejected (except for paediatrics).

*"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. Such information on clinical trials should be concise, clear, relevant and balanced and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures). In the exceptional 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.*

*Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype."* . [1, pp. 19–20]

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].

Moreover, the SmPC Guideline section 4.1 [1, p. 7] states:

*"Where results from subsequent studies provide further definition or information on an authorised indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1."*

The guide for assessors on the "Wording of therapeutic indication" [5] , states:

*"It is important to note that any supplementary data provided in section 5.1 is to be considered as additional information aiming to provide further details on the scientific basis of the indication, as presented in section 4.1; it cannot constitute a new indication nor can it be interpreted as a restriction to the indication (e.g. in terms of population characteristics included in clinical trials or possible use in combination therapy)."* However, concepts used in section 4.1. may be defined or clarified in section 5.1.

## *3.3 Structure of 5.1*

The SmPC Guideline [1, pp. 19–20] describes the following 5.1 subsections:

- Mechanism of action (if known)
- Pharmacodynamic effects
- Clinical efficacy and safety
- Paediatric population

## *3.4 Target audience*

Section 5.1 presents information relevant to the prescriber and other HCPs, to support their decision to prescribe the product for an individual patient in the context of the authorised therapeutic indication(s) . [1, pp. 19–20] The information on clinical efficacy will also be used in the discussion between the prescriber and the patient about treatment objectives and expected benefits.

## *3.5 EPAR*

The rationale underlying the opinion on the benefit-risk balance and agreed conditions of use of the medicinal product are described in the EPAR. [5]

The purpose of the EPAR is to reflect the data that were the basis of the approval decision, the reasoning regarding the balance of benefits and risks, and any extrapolations, restrictions or conditions of the marketing authorisation. [6] The EPAR is intended to be a comprehensive and transparent source of information for stakeholders [7].

A link to the EPAR is foreseen in the SmPC Guideline. [1, p. 3] 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. In section 10 of the SmPC, reference is made to the agency website.

### *3.6 General principles for the assessment of Section 5.1*

- The information should be concise and limited to information relevant to the prescriber. The information should also be statistically compelling.
- 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 information on off-label use.
- Consistency within a class and the therapeutic area is recommended.
- The promotional use of adjectives, adverbs should be avoided, e.g., very strong effect and high affinity. Also, value statements like "clinically relevant" should be avoided.

Information not suitable for section 5.1 may be relevant to be reflected in the EPAR provided it falls within the scope of the EPAR.

# 4 Mechanism of action

Under this heading, the molecular basis of the pharmacological activity of the active substance and a brief description of how this primary effect initiates and leads to the intended clinical effects is provided. In this sense, it provides a pharmacological rationale for the therapy for the target population in the authorised indication(s).

Important principles are:

- Information in this section is usually based on in vitro and pre-clinical data, whereas the main clinical findings are presented with the results of the major clinical trials and are therefore out of scope of this subsection.
- Description of the first molecular event, for example, binding to the receptor, should be included, together with subsequent secondary events if relevant for the clarity of the mechanism of action. A direct relationship with a functional endpoint may be included when established.
- Animal data are needed only where they contribute to the understanding of the mode of action. Efficacy in animal models or description of additional favourable effects is usually superseded by beneficial effects in humans (to be described later in 5.1) and is considered superfluous. If more clinical data describing the mechanism of action becomes available during the product's lifetime, the pre-clinical paragraphs may become less relevant and should be reconsidered.
- In case of a limited understanding of the mode of action, this should be clearly stated in this part of the SmPC.

# 5 Pharmacodynamic effects

The subsection "Pharmacodynamic effects" should be concise and focused on the essential information that is relevant for the target population and to prescribers. For anti-infectives, microbiological data (e.g., about mechanisms of resistance) may be the most important data for efficacy. Clinical data, based on therapeutic exploratory (phase 2) studies, e.g., on appetite or energy expenditure in weight management, may support the mechanism of action.

Considering that the previous subsection may inform in general terms on the pharmacodynamic effects when describing the mechanism of action and that relevant favourable effects can be reflected as part of the main results of the clinical trials, the contents of this subsection could focus on other

pharmacodynamic effects explaining safety issues (such as QT prolongation) that have been identified or excluded by a clinical trial.

Assessment principles:

- Important pharmacodynamic effects observed in humans, based on convincing clinical data and relevant for the authorised indication(s) may be included in this section. This includes the results of specifically designed therapeutic exploratory studies (Phase 2 pharmacodynamic studies). The presentation is usually qualitative, and tables are not expected.
- Secondary pharmacodynamic effects observed in humans with relevance to safety can be mentioned here if this contributes to the understanding of adverse reactions, warnings and contraindications mentioned elsewhere in the SmPC. Details about adverse reactions are described in section 4.8.
- Non-clinical information is not expected to be included: Favourable pharmacological effects observed in animals are usually irrelevant and superseded by clinical data. Unfavourable pharmacological effects observed in animals relevant for safety should be included in section 5.3 if this information is considered relevant for the prescriber and is not addressed in other sections (e.g., 4.4).

The effect on QT(c) duration should be described in 5.1, together with the basis of the information (e.g., thorough QT trial), also if there is no effect on QT.

Unintended immunogenicity without identified effect should be described here in section 5.1 [→6.12].

# 6 Clinical efficacy and safety

## *6.1 General approach*

The information in this sub-section of 5.1 defines the characteristics of the product with respect to efficacy as agreed by the CHMP. Thereby, it facilitates the decision to prescribe a particular medicinal product for a particular patient in the context of the authorised therapeutic indication(s). Helpful information on clinical trials is concise, clear, relevant, and balanced and summarises evidence from relevant studies supporting the indication. [1, pp. 19–20]

Only information that is related to the authorised indications can be included. Claimed product characteristics should be relevant for prescribers and sufficiently substantiated, e.g., a rapid onset of effect. The information provided in section 5.1 should be presented neutrally and factually.

All statements and results included in section 5.1. should also be reflected in the EPAR. To facilitate cross-reference to further information, trial data presented in section 5.1 should include a unique identifier. Most helpful may be the acronym of the trial, unique identifiers such as EUDRACT or first author and publication year (for references in bibliographic procedures). It is not in the remit of the SmPC to give general advice on the treatment of medical conditions References to therapeutic, and clinical practice guidelines should therefore not be mentioned.

## *6.2 Patient characteristics*

The prescriber may want to determine whether a patient resembles the studied population sufficiently to support the relevance of the study results to this particular patient. This implies focusing on the patient characteristics that might be predictive for the therapeutic effect and that listing all inclusion and exclusion criteria is inappropriate. Important aspects are age and gender, and to what extent the de facto studied population covers the full spectrum/stages of the condition, information on important subgroups [→6.4.6] and important prior/concomitant treatments (particularly if the indication refers to such).

Specific diagnostic tests applied for the inclusion of patients, e.g., pharmacogenomics criteria or companion diagnostics, are to be included [→6.7.2].

## *6.3 Estimand*

Appropriate estimands are usually the main determinant for aspects of trial design, conduct and analysis. The description of estimands should be kept focussed and understandable. While the description of estimands should be aligned with guidance [8], use of technical language should be avoided as well as mentioning the term 'estimand'.

A treatment policy estimand has been considered most valuable for regulatory decision making and is therefore most often chosen as primary estimand for analysis. This will then most often be the basis for the discussion in section 5.1.

Alternative estimands (e.g., a hypothetical estimand) may provide complementary information by separating "what can be reached" from discontinuations. Regulatory experience with such estimands is limited, and there are still many concerns as hypothetical estimands do not reflect a true result but rather an idealised situation. If proposed for inclusion in section 5.1, the alternative estimand should have been pre-specified and included in the type-1 error controlled testing hierarchy. Discontinuations should be quantified.

## *6.4 Efficacy results*

### 6.4.1 What should be presented and what may be presented?

Results presented should be (clinically) relevant to the prescriber. [1, pp. 19–20]

Results should also be statistically compelling. [1, pp. 19–20] 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. Predefinition of the endpoint within a statistical testing procedure that controls the type 1 error and a statistically significant result according to this procedure [9] provides the strongest - but yet not the only - methodologic support for the inclusion of an endpoint in section 5.1. In exceptional cases, several other important methodological aspects are considered for the acceptability of the result, e.g., its robustness in terms of aspects like consistency within the trial and with external data, the validity of the statistical test and the estimation method applied, but also objectivity of an endpoint in relation to the trial design.

Uncertainty should be reflected; usually, 95%-confidence intervals for the treatment effect size are considered appropriate for this [→6.4.5].

The same principles apply before and after authorisation.

### 6.4.2 Endpoints

Usually, the results of the primary endpoint will be presented.

For composite endpoints, the components can be presented, if these are non-competing or if meaningfully analysed separately. The presentation of components may be particularly relevant in the setting of composite rank-based endpoints that are clinically difficult to explain.

Secondary endpoints [10] may be used to contextualise the effect on the primary endpoint in terms of clinical benefit, e.g., by complementing objective measurements by PROs reflecting the clinical impact. This requires, that such endpoints are clinically relevant, results are distinctive, methodologically

robust and informative, and the endpoint is assessed to include information that is not covered by the primary endpoint.

In general, inclusion of a large number of 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. 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.

Still, it may be of value to present secondary endpoints that may be correlated with the primary (and key secondary) endpoints if such endpoints are commonly reported in the therapeutic area, and results are robust.

Subgroup or post-hoc analyses should be mentioned only under circumstances described in [→6.4.6].

If a non-significant endpoint is considered reportable, it is encouraged only to report the central tendency (e.g., mean or median) of treatment effects with confidence intervals. This may be relevant for endpoints such as mortality or, in the case of orphan diseases where (at the standard level), non-significant effects in primary endpoints might be acceptable to support efficacy. Other endpoints may additionally be suggested for inclusion by CHMP, if results are judged to be informative for the prescriber, based on clinical relevance and importance in the therapeutic field. A statement of lack of statistically significant difference, aiming to implicitly claim equivalence, is not acceptable because it is methodologically flawed.

A balanced representation of the information also reports the negative results if a development program includes both positive and negative trials.

### 6.4.3 How to present

Emphasis is on the treatment effects exerted by a product, i.e., differences between treatment arms in controlled trials. Appropriate measures of uncertainty should accompany point estimates. Confidence intervals are considered more informative than standard errors. A description of the statistical model and test applied is rarely necessary in the text, but it should be added in the footnotes of tables. If applicable, it is recommended to present baseline values, changes from baseline values, differences between study arms, and the corresponding point estimate and confidence interval of the difference in tables. 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. For the most important time-to-event analyses, Kaplan-Meier curves should usually be provided.

Information on treatment and/or study discontinuation rates in each arm should be presented when this is non-negligible.

Redundancy should be avoided in presenting the same information in text and tables or figures and as multiple endpoints that essentially show the same clinical effect.

### 6.4.4 Alternative presentation of endpoints and alternative endpoints

Exceptionally, the primary endpoint or an important secondary endpoint in the trial is not optimal for informing the prescriber. As outlined above [→3.1], the SmPC is the basis of information for healthcare professionals on how to use the medicine safely and effectively. Therefore, although the original primary endpoint will be the starting point for considerations on presentation, there are cases where CHMP may consider another endpoint more relevant to the prescriber. In such cases, this could also be the basis for description in 5.1. In line with below [→6.4.5], the original (inferential) endpoint could be

mentioned in text, with an alternative presented in the table (specifying that it is not the primary endpoint).

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) on the same VAS in each treatment arm. Presentation of responder rates, using established indisputable 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)").

Arbitrary and selective presentation of the best results should be avoided. The choice of endpoint(s) to be presented in section 5.1 should be explained in the EPAR.

### 6.4.5 Confidence intervals and p-values

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, and the presentation of p-values should be restricted to the EPAR, where their role in decision-making can be presented more clearly.

Usually, a range of endpoints is investigated in associated analyses. After the trial has been conducted there are two types of results/endpoints: a) those endpoints for which a statistically significant treatment effect has been demonstrated according to a pre-defined confirmatory testing strategy versus b) all others, for which statistical significance cannot be declared (the latter comprise endpoints that had not been tested or for which statistical significance could not be shown, and the presentation of these is therefore to be seen in a more exploratory/descriptive sense). This distinction should be made apparent in section 5.1.

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. Those endpoints are usually described in-text provided the magnitude of the treatment effect is indeed also relevant from a clinical point of view. To underline the level of confirmatory information retrieved from the clinical trial in these cases, the (adjusted) confidence intervals, which provide the precision of the treatment effect shown, should be given. By this, while not presenting p-values directly, the scientific conclusions and the underlying inference, including the statistical testing procedure that controls the type 1 error, are incorporated in the SmPC while focussing on those elements that the prescriber may use for the treatment decision. In addition, the term "statistically significant" can be used.

Of note, depending on the testing strategy applied in the trial and in case endpoints were tested at a different significance level than 5% two-sided, this presentation of adjusted confidence intervals from the trial and the decision making therein can differ from the information describing the product using 95% confidence intervals given in tables [→7].

The inferential analyses of a trial should be presented and remain at the level of maturity that was relevant for the inference. Along with these data, updated or final analysis may also be relevant to present. [→6.14] 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.

If reportable [→6.4.2], those endpoints not (successfully) tested significantly within a pre-defined confirmative testing strategy should be declared as such and should only be described descriptively,

and point estimates together with 95% confidence intervals can be given. This is expected to apply primarily to survival data, and judgements like "similar" or "higher" should be avoided.

Point estimates and confidence intervals should preferably be presented in tables for important endpoints. While the conventional way for presentation for all endpoints not tested is to present 95% confidence intervals, the alignment with multiplicity adjustment is less obvious for the endpoints tested in a confirmatory manner. Nevertheless, to inform the prescriber and to ensure consistency of information to other endpoints, it is considered best to describe the product in the same manner for all endpoints, i.e., providing 95% confidence intervals for the treatment effect where the product is described, e.g. in these tables. A footnote to this table should explain this.

In some cases, the meaning of a 95% confidence interval may not be obvious, e.g., with non-parametric tests or rank analyses. In such cases, other metrics clarifying the uncertainty may also be cited. When adjusted confidence intervals are reported for formally significant endpoints, the unadjusted 95% confidence intervals should be given with an explanation of the difference.

### 6.4.6 Subgroup analyses, exploratory analyses and post-hoc analyses

For the SmPC, highlighting the consistency of effects, or lack thereof, in section 5.1 can be done only where it represents essential information to understand the benefit/risk in specific subgroups. Where important uncertainty or known differences in the treatment effect exist in or between key subgroups despite overall positive findings, this can be expressed in a warning in section 4.4 of the SmPC, with data presented in section 5.1 if considered useful to the prescriber. 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, 4.3 or 4.4 of the SmPC, as appropriate. [11, p. 20]

In cases when clinically relevant information from subgroup or post-hoc analyses is presented in 5.1, it should be identified in a balanced manner reflecting the limited robustness of both positive and negative secondary observations. [1, pp. 19–20] There should be a clear rationale for the inclusion of such analyses. In some cases, subgroup analyses are included in a confirmatory statistical testing strategy, which may result in statistically compelling and clinically meaningful efficacy claims. In such cases, outcomes in the complementary subgroup that is part of the authorised indication, will also be relevant. Furthermore, also the CHMP may ask the inclusion of subgroups, notably in case not all subgroups exert the same level of efficacy. [11, p. 17] The reasoning for presenting or not subgroup analyses in section 5.1 should be justified in the EPAR.

Relevant subgroups could be those that affect the decision of prescribing, e.g., when the benefit/risk may be different, dose recommendation may be different, or sensitivity for adverse reactions may be different. Correspondingly, when formal evidence as defined by pre-specification and statistical significance is absent, a decision to nevertheless include the data in the SmPC implies that the regulatory evaluation has accepted the results to be sufficiently methodologically compelling to potentially impact the prescription of the drug.

In line with the paediatric regulation, reflected in the SmPC guideline in recommending that "the results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented", relevant results in paediatric subgroup(s) should be presented, whether positive or negative. [→6.6]

Elderly are the main users of many medicines. Pharmacokinetics in elderly may differ from younger people and elderly may be more sensitive to pharmacodynamic effects. Therefore, the number or proportion of elderly included in the major trials may be cited when describing the main characteristics of the studied population, especially if they are an important part of the target population. If any

difference in effect is identified in elderly, it should be communicated and quantified in a balanced manner along with a warning in 4.4 if deemed necessary to warn HCPs. If no difference in efficacy has been identified, this may be communicated as long as available evidence is considered robust. Detailed information on available data and reasoning for elderly information in SmPC should be presented in the EPAR.

In case the indication/target population is restricted to a subgroup of a trial population, the main results of the inferential analysis of the study should be presented in text, despite the fact that this metric includes patients for whom the product is not indicated. This is since the inference of any efficacy depends on this metric. In tables and graphs, the results in the authorised indication/population should be presented; the text should clarify that these are subgroup results.

### 6.4.7 Pooled analyses

Usually, individual trials are the main basis of the information on a particular medicinal product, especially in the initial SmPC at the time of approval. If there are multiple studies relevant for the same indication, an integrated summary could be considered, for example pooling the results of the studies or meta-analysis instead of presenting the most important studies separately. This requires, however, that pooling of trials is clinically and statistically applicable and adequately documented and reflected/explained in the EPAR. For the appropriateness of pooling study results, reference is made to respective EMA guidance [12].

### 6.4.8 Patient-reported outcomes (PROs)

The assessment of PROs is not different from other endpoints in the general case. PRO claims should be based on type 1 error-controlled analyses.

Thus, for PROs, the general requirements for the inclusion of results apply [→6.4]. This also applies to Quality-of-Life assessments, a subtype of PROs. The general guidance ('clinically relevant and statistically compelling') remains valid. [1, pp. 19–20] [→6.4.1] To establish clinical relevance, the effect size should exceed the pre-defined 'minimal clinically important difference', which should in itself be well-justified on a clinical basis a priori. For equivalence claims, appropriate methodology should be pre-defined. PRO instruments should be adequately validated. A component or subset of a validated scale should be considered a new instrument that requires its own validation.

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. If clinically relevant, statistically robust, and informative, the results can be reflected in 5.1, and no other sections of the SmPC are appropriate.

Since PROs are often overlapping, only the most representative of several measures should be included even if many measures would have shown relevant and methodologically robust results. Inclusion of several PROs measuring in essence the same endpoint would exaggerate the real effect on Health-related Quality of Life (HRQoL).

If it is considered important to include an unfamiliar PRO in 5.1, it may be considered to present the data as a responder fraction or a time-to-event measure rather than as a mean treatment effect [→6.4.4]. The choice should be justified in the EPAR. Specific guidance about PROs should be followed. [13] [14]

### 6.4.9 Graphs

Visualisation of data is helpful to many readers. The shape of, e.g., Kaplan-Meier (K-M) curves may be essential for understanding the drug effect. In graphs, the same principles should be adhered to as for information provided in text and duplication of data should be avoided. The following issues should be considered:

- The graph should be balanced and not promotional. The limits of the y-axis should be noted, and colours and shading of bars. Overly fancy formatting should be avoided.
- The tradename should not be used, but the international non-proprietary name (INN) or if not existing the common name.
- Following the discussion above, p-values should not be presented in graphs. Annotations to claim statistical significance (*, **, ***) or significance of endpoints (timepoints) should not be made and should not duplicate information in text or tables. It is encouraged to include the number of subjects and 95% confidence intervals or other relevant uncertainty measures in the graphical presentation.

In the case of multiple key outcomes, e.g., constituting time-to-event endpoints where K-M curves are presented, an effort to limit the presentation of graphs to one per indication should be pursued in order to keep the SmPC readable (e.g., if mature overall survival (OS) data are available, present OS K-M curves, and omit progression-free survival (PFS) curves (depending on the shape of the curves). Only reasonably mature K-M curves should be presented in the SmPC, since immature curves may be misleading, e.g., by only reflecting a subgroup with early events. Presentation of immature K-M curves as a cautionary measure, e.g., if a detrimental trend is observed, may be required.

Forest plots can be considered a concise way to present information on subgroups [→6.4.6], or on components of composite endpoints or other endpoints, especially in cases where the results clearly differ from the main analysis and are assessed as relevant for inclusion in the SmPC.

Individual patient results (waterfall plots etc.) should be avoided, being too granular/ detailed information for the SmPC.

### 6.4.10 Single-arm trials

Single-arm trials (SATs) can be described in section 5.1, where these are the only or major data sources available to support the indication. 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). Measures that are affected by prognosis, such as median overall survival (OS) or progression-free survival (PFS) in oncology, do not isolate a drug effect and are not suitable for section 5.1. Likewise, measures such as stable disease or disease control rate should generally not be included for the same reason.

When ORR is the primary endpoint, the presentation of "duration of response" (DOR) is also required to understand the relevance of the observed ORR.

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. [→6.15.2]. It is recommended in a SAT to refrain from statistical claims. In any case, point estimates and confidence intervals should be provided.

### 6.4.11 SI-units

Measurements should be expressed in SI-units with "conventional units" between parentheses if both units are still common in the Union. [15]

## *6.5 Safety results*

Safety information is presented in other SmPC sections (mainly 4.8 and 4.4).

If a major trial has been specifically carried out to characterise a safety concern or if pre-specified endpoints or clinical outcomes from major trials pertain to safety, this can be reported in 5.1 following the abovementioned criteria about clinical relevance and statistical robustness. However, the interpretation in terms of safety information and risk mitigation is to be addressed in sections 4.4 and 4.8 (e.g., "4.8 (c) Description of selected adverse reactions"). Mutual cross-references between 4.4, 4.8 and 5.1 should be included when applicable.

Another reason to include safety-related information could be that pharmacodynamic information predicts certain risks [→5], independent of whether these have been observed (e.g., QT-prolongation). Also in this case, appropriate cross-referencing to relevant sections of the SmPC is expected.

## *6.6 Paediatrics*

For exploratory (including pharmacokinetic/pharmacodynamic) studies, the results of the main endpoints should be given with the main characteristics of the population studied and the doses used, even if such results are inconclusive. This also applies to indications or doses that are not authorised. When they are available, information and results of confirmatory studies should usually supersede and replace those of exploratory studies. For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patients), and the main results regarding pre-specified endpoints should be provided, whether positive or negative. If data are considered inconclusive, this should be stated. [1, pp. 19–20]

This implies that, in contrast to adult studies, all relevant paediatric (pharmacodynamic and efficacy) studies should be reported in section 5.1. [1, pp. 19–20] [16] [17] [18] It is important to highlight that such presentation of information is not per se equivalent to a demonstration of efficacy.

To streamline the presentation of paediatric safety information and align it with the general principles for presentation by section, all paediatric safety information should be presented in 4.8 (if applicable, highlighting that this refers to off-label use), and efficacy should be described in 5.1 (independent of whether an indication is authorised). Although safety information on off-label use will be included in 4.8, this information should not be included in the PIL. The study description in section 5.1 should have a unique identifier to be mentioned in the cross-reference in section 4.8.

## *6.7 Diagnostics*

### 6.7.1 The SmPC of a diagnostic agent

Trial results can be described in analogy with therapeutic agents. The description of the operative characteristics of the diagnostic, should be such as to allow for an interpretation of the additional value of the diagnostic procedure. The information should focus on the diagnostic agent (e.g., a radiologic contrast agent), whereas information on the technique (CT-scan with contrast compared to nuclear imaging) may be described more appropriately elsewhere (documentation of the radiology device, textbooks, etc.).

### 6.7.2 (Companion) diagnostic tests in the SmPC of a therapeutic agent

In some cases, specific diagnostic tests are used to identify patients who are suitable or unsuitable for the therapy. The test employed in a trial should be included by brand name in 5.1 together with the population description of the trial. The brand name should however be omitted from other sections of the SmPC. The user documentation of the diagnostic test is the appropriate place to describe conditions for which it was validated and to describe relevant trial results.

### 6.7.3 Software for use with diagnostic agents

In some cases, specific software is used to facilitate the evaluation of results obtained using a diagnostic agent (such as a contrast agent). If there may be differences between the performance of software of different authors, the package employed in a trial can be included by brand name and version and the description of the trial method. The brand name should however be omitted from other sections of the SmPC. The user documentation of the software is the appropriate place to describe diagnostic agents for which it was validated (which should be confirmed by the notified body); other sections of the SmPC should preferably refer to the software documentation.

## *6.8 Therapeutic class-specific guidance*

Detailed information regarding the contents of section 5.1 can be provided in class-specific guidance, such as for antibiotics [19] and numerous blood products [20]. In such cases, a pre-defined structured format is preferred. The information can be included in a specific document describing specificities regarding the SmPC in a therapeutic class, or it could be part of class-specific assessment guidance (as with antibiotics, blood products).

While maintaining consistency within a therapeutic class is important, each assessment should be product specific and the aim should be to maintain only the information that is important for the prescriber.

## *6.9 Combination therapy*

In case of a combination therapy involving a substance (X) and another medicinal product (Y), the appropriate use of Y may need to be described in section 4.2 of X. Moreover, its use in the study should be included in the trial description in section 5.1 of X.

When a product (Y) that has been used in combination with another, still existing product (X), is withdrawn from the market for reasons not related to safety, the SmPC (including 5.1) of the remaining product (X) may be left unchanged if still relevant.

## *6.10 Hybrid application*

Section 5.1 content for a hybrid with a bridge to clinical data primarily follows the reference medicinal product if the indications, route of administration, and strengths do not differ. In other words, the information from the reference product's SmPC that applies to the hybrid (as evidenced by bridging to clinical data) will be included in 5.1 of the hybrid. Data submitted for bridging to the reference product should be described in the EPAR and should usually not be included in section 5.1.

All contents of section 5.1 should be justified in the clinical overview by the Applicant / MAH. Based on sound justification, the applicant may include additional information in the hybrid's section 5.1. If the hybrid includes, e.g., a new indication, the whole 5.1 may be unique for the new product.

## 6.11 Biosimilars

Section 5.1 content for a biosimilar should be in all relevant aspects consistent with that of the reference medicinal product (except for indications or dosage forms still covered by patent law), if they do not differ in terms of indications, strengths, pharmaceutical forms or routes of administration [21] [A]. None of the results from the comparability exercise (including phase 3 efficacy/safety trial results and phase 1 PK results) are relevant for the SmPC.

The description of immunogenicity in the SmPC should not include concrete anti-drug antibody (ADA) rates (%). This is because the bioanalytical methods used are different for the reference medicinal products and the biosimilars; hence, the ADA rates are not comparable. Nevertheless, immunogenicity comparison is essential for most biosimilar developments; therefore, the actual ADA rates seen in the clinical studies within the comparability exercise should be reflected in the EPAR.

## 6.12 Immunogenicity

If immunogenicity data is an endpoint or a mean to demonstrate efficacy (e.g., vaccines), such data can be described in section 5.1. 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.

Anti-drug antibodies, with an effect on safety or on efficacy, will usually be considered an adverse drug reaction to be described in sections 4.8 and/or 4.4.

Unintended immunogenicity without identified effect should be described in section 5.1 (subsection on pharmacodynamics effects) using the standard statement: "Anti-drug antibodies (ADA) were <very rarely> <rarely> <uncommonly> < commonly> <very commonly> detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. <however, data are still limited.>"

## 6.13 Extrapolation

Section 5.1 provides efficacy results from clinical trials considered important for prescribing physicians but does not include the justification of a positive benefit/risk conclusion in the authorised indication. [→3.5] By definition, extrapolation extends the inference based on clinical trial data beyond the population that was investigated. Therefore, the justification of the extrapolation would be expected in the EPAR rather than in the SmPC. If CHMP or the applicant consider that the extrapolation entails relevant uncertainty, this could be communicated as a warning in section 4.4. Similarly, results of modelling and simulation that are the basis for the recommended dose, should be described in the EPAR only.

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 if the information supports efficacy and safety of the new route of administration. The same applies when a new fixed- combination medicinal product is authorised, where the new approval is based partly on extrapolation from the individual components.

## 6.14 Interim analysis and updated data

In case approval is granted based on an interim analysis rather than the analysis of the full data of a trial, the results of the inferential interim analysis will generally be described in 5.1, together with adjusted 95% confidence intervals in text; however, it is expected that results from later analyses will be provided in tables as soon as they become available, replacing the interim data, to ensure that the

most informative data (most patients, longest observation) are covered in the tables. [→6.4.5]. The pre-defined strategy to control the type 1 error rate should be considered as much as possible.

## *6.15 Observational studies*

### 6.15.1 Evidence from use of the product

Real world evidence is evidence obtained from real world data, which are observational data obtained outside the context of randomised controlled trials and generated during routine clinical practice. 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. This does not preclude inclusion and discussion in the EPAR, as for other data submitted.

### 6.15.2 Data for external or historical controls

Potentially biased observational data should not be included in the SmPC, e.g., to contextualise the treatment effect in SATs. Such information can be presented in the EPAR. Noting that it should not prevent the presentation of results of a SAT [→6.4.10], the three main reasons not to include external control data in a SmPC are:

- the two sets of results are based on different sets of data and methodological approaches, which need to be fully described and carefully considered before any comparison (apart from methodological skills, the extent of information to be provided would be incompatible with concise information as expected in a SmPC),
- information in SmPC should be product specific only,
- it would prevent debate or need for update in case new observational data emerge which would differ from the previous observations and challenge the comparison (especially if they are presented by a competitor).

# 7 Example

An example is provided below where several confidence intervals are presented for the same endpoint (overall survival). In this example, the primary OS analysis (confirmatory hypothesis test) is performed at the interim analysis, while the final study data are also available. In addition, a descriptive presentation is provided for a secondary endpoint (confirmed objective response).

The primary endpoint was overall survival at a planned interim analysis after 413 events, which occurred after a minimum follow-up of 13.2 months. The trial demonstrated a statistically significant improvement (based on the O'Brien-Fleming interim analysis boundary) in OS for patients randomised to active treatment. Mortality was 190/292 (65.1%) for active treatment and 223/290 (76.9%) for control. The estimated hazard ratio was 0.73 with a multiplicity-adjusted 95.92% CI of (0.59, 0.89) that ensured study-wise type I error control at two-sided 5%. Other efficacy endpoints were exploratory only.

**Table X provides results in the Full Analysis Set after a minimum follow-up of 24 months.**

| | Active (N=292) | Control (N=290) |
|---|---|---|
| Overall survival[a]<br>Mortality events n (%)<br>Hazard ratio (95% CI)[b] | <br>250 (85.6%)<br>0.70 (0.58, 0.83) | <br>279 (96.2%) |
| Confirmed objective response<br>(95% CI) | 19.5%<br>(15.1, 24.5) | 12.4%<br>(8.8, 16.8) |

[a] Of the patients randomised to control, 17 (6%) crossed over at any time to receive active treatment.

[b] Results from proportional hazards model adjusted for prior maintenance therapy and line of therapy. 95% CI are not adjusted for multiplicity.

# 8 References


[1] EC, 'A guideline on summary of product characteristics (SmPC)', Sep. 2009, Accessed: Nov. 14, 2022. [Online]. Available: https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

[2] EMA, *EMA scientific guidelines*. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines

[3] EC, *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*, vol. 311. 2001. Accessed: Nov. 30, 2022. [Online]. Available: http://data.europa.eu/eli/dir/2001/83/oj/eng

[4] EMA (Stakeholders and Communication Division), 'Annex 3', in *Consolidated report on the activities of topic groups established in 2015*, vol. EMA/225307/2017, 2017. [Online]. Available: https://www.ema.europa.eu/documents/annual-report/consolidated-final-report-activities-patients-consumers-working-party-healthcare-professionals_en.pdf

[5] EMA, 'Wording of therapeutic indication - A Guide for Assessors of Centralised Applications', p. 3, Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/wording-therapeutic-indication-guide-assessors-centralised-applications_en.pdf

[6] EMA, 'European public assessment reports: background and context'. Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context

[7] P. Papathanasiou *et al.*, 'Transparency in drug regulation: public assessment reports in Europe and Australia', *Drug Discovery Today*, vol. 21, no. 11, pp. 1806–1813, Nov. 2016, doi: 10.1016/j.drudis.2016.06.025.

[8] ICH, 'ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials'. Feb. 17, 2020. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

[9] EMA, 'Points to Consider on Multiplicity Issues in Clinical Trials', Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-multiplicity-issues-clinical-trials_en.pdf

[10] ICH, 'ICH E9 Step 5 - Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)'. Sep. 1998. [Online]. Available: https://www.ema.europa.eu/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

[11] EMA, 'Guideline on the investigation of subgroups in confirmatory clinical trials', [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf

[12] EMA, 'Points to consider on application with 1. meta-analyses; 2. one pivotal study', p. 7, 2001, [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-application-1meta-analyses-2one-pivotal-study_en.pdf

[13] EMA (CHMP), 'Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQoL) measures in the evaluation of medicinal products'. Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation_en.pdf

[14] EMA, 'Guideline on the evaluation of anticancer medicinal products in man, Appendix 2', p. 18, [Online]. Available: https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf

[15] EC, *Council Directive 80/181/EEC of 20 December 1979 on the approximation of the laws of the Member States relating to units of measurement and on the repeal of Directive 71/354/EEC*. 1979. Accessed: Nov. 14, 2022. [Online]. Available: http://data.europa.eu/eli/dir/1980/181/2009-05-27/eng

[16] EMA, 'Paediatric Regulation', European Medicines Agency. Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation
[17] EMA (SmPC Advisory Group), 'presentation-summary-product-characteristics-guideline-paediatric-aspects_en.pdf', p. 11, Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/documents/presentation/presentation-summary-product-characteristics-guideline-paediatric-aspects_en.pdf
[18] EMA (SmPC Advisory Group), 'Section 5-1 Pharmacodynamic properties - SmPC training presentation', p. 16, [Online]. Available: https://www.ema.europa.eu/en/documents/presentation/presentation-section-51-pharmacodynamic-properties_en.pdf
[19] EMA, 'Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections', p. 30, [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf
[20] EMA, 'Clinical efficacy and safety: blood products (including biotech alternatives)'. Accessed: Nov. 14, 2022. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety/clinical-efficacy-safety-blood-products-including-biotech-alternatives
[21] EMA (Human Medicines Evaluation Division), 'QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product'. Jun. 18, 2018. Accessed: Nov. 29, 2023. [Online]. Available: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-general-principles-regarding-summary-product-characteristics-information/hybrid/biosimilar-product_en.pdf