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Committee for Medicinal Products for Human Use (CHMP)

Methodological Principles for the Assessment of Section 5.1 of the Summary of Product Characteristics

Studies to include and how to describe the study design and results

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Abbreviations

CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
EPAR	European Public Assessment Report
MWP	Methodological Working Party
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics

1. Introduction

The content of section 5.1 ("Pharmacodynamic properties") of the Summary of Product Characteristics (SmPC) is proposed by the applicant or marketing authorisation holder and it is assessed by the rapporteur/s. The final content is discussed by the Committee for Human Medicinal Products (CHMP) and remains a case-by-case decision.

The SmPC Guideline [1] states: "*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 CHMP has frequent discussions on section 5.1, e.g. concerning what trials and what information to include. This document aims to provide tools and details for the drafting and assessment of this part of the SmPC in accordance with the SmPC guideline.

In general, section 5.1 should be limited to the indication/s, population and posology that are authorised. No information should be given on indications or populations that were not applied for or for which there was not a positive opinion. Section 5.1 may provide further information on the authorised indication (e.g. clarification of what staging system for the disease was used). There should be no information on off-label use.

The same principles on deciding what to include apply before and after authorisation.

2. Which efficacy studies to include?

Relevant main information with respect to efficacy of the medicinal product in the intended indication is included in section 5.1. The studies to be included should be limited to those which are considered to provide confirmatory evidence of efficacy. Usually, the confirmatory evidence is provided by one or several randomized trials, or occasionally one or several single arm trials. In exceptional cases, results from other sources than clinical trials are considered relevant for confirmation of efficacy.

Efficacy results from methodologically reliable supportive studies generated before or after authorisation of the indication may be briefly summarized, if they add relevant information for the prescriber (for example related to patient populations excluded from the pivotal studies or relevant endpoints not captured in the pivotal trials, e.g. outcomes with low incidence). In situations where pivotal evidence of efficacy comes from one or more positive studies, it is generally not considered necessary to include non-informative studies conducted in the same, or overlapping indications for the sake of transparency or comprehensiveness. If at time of opinion the CHMP has requested a post authorisation study to confirm the (long term) efficacy or effectiveness, once available these results should be described as well if considered relevant and reliable.

Usually, individual trials are the main basis of the information. In some instances, pooling of results from multiple studies may be considered for inclusion in section 5.1, for example for endpoints with low event counts.

For all trials, only results which have been assessed to be both clinically relevant and methodologically reliable should be included. Methodological reliability means that the results can support an interpretation with an estimable and acceptable level of uncertainty. Results which are not methodologically reliable should not be included because these are likely to lead to an incorrect interpretation, even when the endpoint in question is considered clinically relevant.

Only information that is related to the authorised indications can be included. Results considered to be a consequence of the effect in the authorised indication but not a separate indication (e.g. cardiovascular outcomes as a consequence of weight management, or prevention of pneumonia as a consequence of prevention of influenza) may be added if deemed relevant for the prescriber.

A comprehensive assessment of all studies included in the clinical development program and details of the assessment and accompanying justification are provided in the European Public Assessment Report (EPAR).

2.1. Comparative studies

Inclusion of actively compared efficacy data in section 5.1 may be acceptable. The included information should be qualified as "main trials" based on robustness and clinical relevance. Ideally, CHMP scientific advice would support both the comparator as relevant and evidence-based as well as the planned/conducted statistical analysis.

2.2. Paediatric population

In contrast to the extent of information presented in adult population, all clinically relevant paediatric pharmacodynamic and efficacy studies are recommended to be reported in section 5.1. Such presentation of information is not *per se* equivalent to a demonstration of efficacy (or safety).

In case of application for and authorisation of an indication in paediatric population, the same principles in terms of methodological reliability as for studies in adult population apply to how the information should be presented in the section 5.1. When results of paediatric studies are submitted but there is no application for an indication in paediatric population or it is not granted as the outcome of assessment, the description of the results, whether positive or negative, needs to be considered for inclusion.

In all situations, the description of results should be done with caution, in particular in case of negative or inconclusive results and it should be ensured that the results, as presented, support an adequate interpretation. Depending on the message, most appropriate may be descriptive text, simple descriptive statistics (e.g. point estimate with CI) and/or a tabular/graphical presentation. It may also be recommended to include text to support correct interpretation and/or highlighting inconclusiveness of the results. In some cases, statement on the overall outcome of the study may be sufficient.

When they are available, information and results of confirmatory studies should usually supersede and replace those of exploratory studies, also when exploratory studies are part of Paediatric investigation Plan. Relevant results in paediatric (sub)group(s) should be presented, whether positive or negative, when applicable.

Note that access to the paediatric reward may depend on inclusion of (some) paediatric data in section 5.1.

3. How to describe the trial design elements and results?

Reporting in section 5.1 should focus on relevant results from trials rather than on a description of what a trial aimed to estimate.

Results for the estimand of highest relevance for patients and benefit-risk assessment according to CHMP assessment should be reported. This estimand is often but not necessarily the pre-specified primary estimand.

A precise description of attributes of the estimands should not be included in section 5.1, however, attributes important for the understanding of the results should be described. In particular, the endpoint and important disease characteristics of the population studied should be described.

Reporting frequencies of intercurrent events and how these were considered in the analysis should generally be restricted to the EPAR, unless this information is of importance for the understanding of the results. Use of technical language should be avoided as well as mentioning the term 'estimand'. Names of strategies to account for intercurrent events such as treatment policy, hypothetical etc. should not be used.

3.1. Treatment

The interventions used in the study need to be clearly described. Treatments received in the clinical trial in addition to the investigational treatments, such as background treatment, combination therapy, rescue therapy and subsequent treatments, should be described in level of detail relevant for understanding the results.

3.2. Population

The population actually included in the clinical trial(s) should be described in sufficient detail to support the understanding and relevance of results. The description may focus on the most important aspects such as age, gender, disease characteristics (e.g. stage) and factors known to be predictive or prognostic of the therapeutic effect.

3.3. Endpoints

Section 5.1 should be limited to information that has been assessed to be both clinically meaningful and methodologically reliable. Hence, section 5.1 does not normally need to include a discussion on reliability of results.

In well-designed clinical trials, confirmatory, multiplicity-controlled endpoints which have reached the pre-defined success criterion are the most reliable results. Some specific situations are further discussed below. Secondary endpoints should be limited to those which are considered to provide additional clinically important information and, therefore, not all secondary endpoints which have reached the success criterion may warrant inclusion.

Descriptive results or other supportive information may be included if deemed relevant to support the interpretation of the endpoints that are included. Ideally, these should have been pre-specified in the statistical analysis plan (SAP). This could be, for example, components of a composite endpoint or distributions of intercurrent events. Furthermore, some model-based methods, such as a negative binomial model, or a log-rank test, do not provide meaningful measures of absolute effects and, hence, need to be supported by descriptive statistics such as annualized rates or Kaplan-Meier median survival time.

3.3.1. Specific situations

The results for the primary endpoint should usually be included unless they are considered not methodologically reliable or not clinically relevant. In the exceptional case that the main evidence of efficacy comes from a formally failed study, results on endpoints assessed as sufficiently relevant and reliable should be included. The justification for the positive opinion should be restricted to the EPAR, but not be included in the SmPC. Some text to support interpretation of the results may be warranted.

In general, confirmatory endpoints which were not statistically significant should not be included because they do not usually support a clear, reliable interpretation that a treatment effect was established. It may not be clear whether results reliably allow to conclude on a negative effect, no effect or a positive trend. There are possible exceptions, such as in rare diseases where adequate power is not feasible, or long-term outcomes. If it is deemed clinically important to include such results and these are considered methodologically reliable, it is important to consider which message is intended to be conveyed with inclusion of these results and include sufficient text in section 5.1 to support correct interpretation.

It is also recommended not to include confirmatory endpoints for which the pre-planned results will become available only with a later data cut. The pre-defined analysis plan should be followed. For example in oncology, if the primary endpoint was progression free survival, based on which efficacy was concluded, it may have been important during the B/R assessment to ensure that there is no detriment in overall survival although the results for the superiority comparison will only become available with a later data cut. In such a situation, the overall survival results should not be included in section 5.1 by default and may be considered case by case. If it is deemed clinically important to include such results and they are methodologically reliable, it is important to consider which message is intended to be conveyed with inclusion of these results such that it cannot be falsely interpreted that a positive, confirmatory efficacy result has been observed. Depending on the message, most appropriate may be descriptive text, simple descriptive statistics, a graphical description or a point estimate with CI. As above, text to support the correct interpretation should be included.

In some specific settings, the pivotal study/ies in the marketing authorization are of descriptive nature only, that is, do not include pre-defined hypothesis testing. If such a study warrants inclusion in section 5.1, it should be carefully considered which results are sufficiently reliable. For single-arm trials, it is of particular importance to consider which endpoints can be interpreted in the absence of a control arm and to include only reliable results which support a clinically relevant interpretation. As an example, although overall survival is a clinically relevant endpoint in oncology, in a single arm trial it is usually not included in section 5.1 because the magnitude of the treatment effect cannot be assessed without a control arm.

3.4. Subgroups

If authorisation concerns a subgroup, the full population studied should be described (see population above). Where a target population is restricted to a subgroup of a trial population, the main findings in the overall trial population should be briefly presented first in section 5.1, followed by the findings in the authorised subgroup. The main focus should be on the results in the authorised indication. No off-label results should be given.

Highlighting the consistency of effects, or lack thereof, in section 5.1 can be done only where it represents essential information to understand efficacy in specific subgroups. The reasoning for presenting the subgroup analyses in section 5.1 should always be justified in the EPAR and follow the principles outlined in Guideline for Investigation of subgroups in confirmatory clinical trials [2]. In such cases, a Forest plot may be appropriate.

If a given population is divided in subgroups (e.g. disease subtypes) and efficacy/safety cannot be ascertained in one of them, leading to exclusion of such subgroup from 4.1, that particular subgroup can be mentioned in 5.1 as part of the population characteristics, i.e., its proportion in the overall population. However, specific efficacy findings from that subgroup are not to be disclosed in 5.1 but described in the EPAR.

If indication is restricted on regulatory grounds, section 5.1. may still present results for the entire studied population. In addition to the results for the studied population, a short textual description of the results corresponding to the restricted indication is to be included.

3.5. Interim analysis, data cutoffs and updated data

The starting point is that the results, and their maturity, submitted as part of the dossier should generally be sufficient for regulatory decision making and, hence, also relevant for health care professionals. Usually, these results correspond to the only timepoint when a null hypothesis for an endpoint was rejected and can be considered confirmatory, as compared to updated results which are normally descriptive in nature and the timing of the data updates often not pre-specified. Furthermore, updated results may be less reliable and may suffer from bias, e.g. as a result of unblinding and cross over. Therefore, the confirmatory analysis, i.e. the data cut when the null hypothesis was rejected, is in most cases the most suitable for inclusion in section 5.1. Based on case-by-case assessment of clinical relevance and methodological reliability, data updates may be included in section 5.1. In this case, only one set of results for an endpoint should be included as two different sets of results targeting the same estimand do not provide additional information and do not serve the purpose of concise information.

If descriptive results for an endpoint have been included in section 5.1 before the hypothesis was rejected (e.g. overall survival) and more mature results are submitted thereafter, these are usually considered relevant for inclusion and should therefore replace the previous data, if they are methodologically reliable.

In general, it is recognized that data updates are mostly considered in the context of time to event endpoints, because it is in the nature of these endpoints that more events become available with longer follow up and interim analyses are often included in studies with time-to-event endpoints.

There are some situations, for example vaccine efficacy over multiple seasons, where the updated results target a different estimand and in this case both results may be included. These should usually also have been defined as separate endpoints in the protocol.

If the product is authorised under a conditional marketing authorisation, section 5.1 should include the relevant and reliable information in the context of the positive B/R and should not mention that efficacy is not comprehensively assessed. Once comprehensive data are available, the content of section 5.1 needs to be re-assessed and it is an assessment issue whether the non-comprehensive results at the time of conditional marketing authorisation are kept in section 5.1 E.g. if the specific obligation was in a different disease setting or with a different treatment regimen, it is likely informative to keep both sets of results. However, if the specific obligation is to collect further information from the same clinical trial, such as more mature data for a clinically relevant endpoint, usually the non-comprehensive results are replaced.

3.6. Summary of the treatment effect in text, tables and figures

How treatment effects are presented can have impact on how they are understood. An appropriate treatment effect estimate should be presented which is usually a comparison between treatment arms. This is usually the summary measure pre-defined in the estimand. The summary measure could for example be the difference in the mean score between the treatment groups compared, or the difference in proportion of patients between the groups who have had meaningful improvement in symptoms. This should be accompanied by appropriate measures of uncertainty which is usually a confidence interval.

Treatment effects may be expressed as relative or absolute effects. If relative effects (odds ratio, relative risk ratio, hazard ratio, relative risk reduction, percentage change etc.) are presented, they should be presented together with corresponding absolute values, including baseline values if applicable, to facilitate interpretation of clinical relevance.

When providing results for an endpoint by study arm, it should be carefully evaluated whether descriptive measures, or model derived estimates are more relevant. Consistency with the estimand and estimated treatment effect are points to be taken into consideration with this respect.

It may also be informative to include additional descriptive measures not directly linked to the treatment effect estimate to support interpretation. The choice of the descriptive measures is context specific and will depend on the nature of the results and the indication. For example, if the endpoint comprises of count data, it may be informative to include e.g. the proportion of patients with no events or an annualized rate of events.

Efficient and informative display of results should be considered if appropriate. For example, in case of two or more similar studies, these may be presented side by side in one table.

Methodological details, such as method of Type 1 error control, do not need to be reflected in section 5.1 because they are not relevant for health care professionals. During the assessment, it has been confirmed that the methods are appropriate and this is reflected in the EPAR.

3.6.1. Confidence intervals and p-values

Statistical significance can be claimed only for tests for which multiplicity was controlled and the null hypothesis was rejected based on pre-defined statistical methodology. If these conditions are fulfilled, statistical significance can be reflected for each endpoint in text or with asterisk in tables. P-values should not be included because the actual numerical p-value does not support clinical interpretation.

In the majority of situations, confidence intervals (CIs) are the most appropriate metric to describe the uncertainty and support interpretation of the results. Clarity of the presentation and consistency of interpretation across studies and endpoints determines the estimates and confidence intervals to be presented. Thus, usually, nominal 95% confidence intervals based on a pre-defined methodology should be included.

Nominal 95% CIs do not always support a correct interpretation consistent with the primary inferential outcomes of the studies. To assess if the presentation of results with such nominal confidence intervals is adequate, study design aspects need to be considered such as situations with relaxed alpha, adaptive design and interim analysis, as well as multiplicity control across subgroups, treatment arms and endpoints. For example, in some studies, the endpoints were not tested with 5% alpha and 95% CI may lead to an interpretation which is not aligned with the results of hypothesis testing. These issues may deserve particular attention especially in the situation where results for endpoints that were not statistically significant according to a pre-defined testing strategy are considered for inclusion in the SmPC.

Overall, it is important to find a reasonable representation of results which supports the correct clinical interpretation while being methodologically reliable and correct. This should be pre-planned in the protocol and the SAP and confirmed during the assessment. The statistical approach used to calculate the CIs should not be described in the SmPC.

3.6.2. Tables

Tables may be appropriate to display results of the main endpoints. Tables should be self-explanatory and should be interpretable independently of the text. It may be helpful to include a description of the treatment regimens in the footnotes of tables, if the treatments are not obvious from the text.

Normally, it is not favoured to include information on the methods applied, i.e. the statistical model, in footnotes. If these are considered necessary for a correct interpretation of the results, it is important that the language of these footnotes is not too technical. Of note, as described above, statistical significance for confirmatory hypothesis tests may be reflected with asterisks in tables, and, hence, asterisks should be reserved for this purpose and other symbols used for other footnotes.

3.6.3. Graphs

Graphs should be included only if they are considered to add relevant information for the prescriber and are sufficiently reliable. Immature Kaplan-Meier curves may be misleading, e.g. by only reflecting a subgroup with early events. For this reason, only adequately mature data should be presented with e.g. Kaplan-Meier curves as evidence for a treatment effect.

If a graph is included, it should present the data in an objective manner that leads to a scientifically sound interpretation, preferably based on predefined methods. An appropriate scale and/or limits of the axes should be used. In graphs, annotations to claim statistical significance (at specific timepoints) should not duplicate information already presented in text or tables and are therefore normally not included. If included, such should be restricted to confirmatory hypothesis tests; a claim of statistical significance cannot be made for nominally significant results that were not formally tested.

It is encouraged to include the number of subjects and 95% confidence intervals or other relevant uncertainty measures in the graphical presentation, especially for aggregated data/relative treatment effect estimates.

Figures should generally not include statistics that were deemed unfit for inclusion in summary tables (e.g. PFS and OS rates when medians are available) nor redundant information that is already available in text or in summary tables (e.g. hazard rates).

References

[1] EC, 'A guideline on summary of product characteristics (SmPC)', Sep. 2009. Available: https://www.ema.europa.eu/en/glossary-terms/summary-product-characteristics

[2] EMA, 'Guideline on the investigation of subgroups in confirmatory clinical trials', EMA/CHMP/539146/2013. Available: https://www.ema.europa.eu/en/investigation-subgroups-confirmatory-clinical-trials-scientific-guideline