Wording of therapeutic indication

A Guide for Assessors of Centralised Applications

I.   Introduction and objectives

This guide has been prepared to support a consistent approach in the process of defining Therapeutic Indication(s) during the assessment of centralised applications for new active substances or new indications.

Recently, the Agency engaged with different stakeholders with respect to the interpretation of the wording of the indication in different therapeutic areas. The therapeutic indication is the primary information on the use of a medicine. It should clearly state the disease/condition and population that a medicine is intended to treat.

Examples of such areas of common interest refer to:

- The description of the target population;

- The severity of the disease;

- The aim of the treatment (diagnostic indication, prevention or treatment);

- The place of the medicinal product in the therapy (e.g. 1st, 2nd line);

- The use in combination therapy;

- The consistency of wording within and across therapeutic areas.

The objectives of this document are:

- To support a consistent approach in the process of defining the therapeutic indication;

- To clarify the regulatory framework surrounding the assessment of the therapeutic indication;

- To provide guidance on the wording of the therapeutic indication in section 4.1 that can be applied across therapeutic areas in order to foster consistency;

- To improve clarity in the understanding of the wording of the indications for stakeholders.

This document should be considered together with other CHMP initiatives and guidance on benefit/risk evaluation, subgroups analyses, extrapolation, and, therapeutic class specific considerations[1].

II.   Regulatory framework

From a regulatory point of view, the therapeutic indication should be clearly stated in section 4.1 of the SmPC to reflect in which disease/condition and target population the benefit/risk balance is established to be positive.

---

1 https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines

The SmPC and the package leaflet (PL) are the basis for information to health care professionals and patients. As per the SmPC guideline[2], section 4.1 of the SmPC should define:

- the target disease or condition, distinguishing between treatment, prevention and diagnostic indication;

- when appropriate, the target population(s), especially when restrictions to the patient population(s) apply (including age groups and, when relevant, particular genotype);

- any mandatory conditions of product usage not covered more appropriately in other parts of the SmPC, when relevant.

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).

In addition, section 4.2 should correlate with section 4.1 in clearly specifying dose recommendations for the entire population covered by the indication. Dose recommendations for populations not included in 4.1 should not be given.

It is important to ensure consistency between information included in the different sections of the SmPC.

As a general principle, a SmPC is product specific and does not have the remit to provide guidance on a specific disease or condition.

At the time of adoption of an opinion by CHMP, the agreed therapeutic indication should be justified as clearly as possible in the Assessment Report.

III. Elements to be considered when assessing the indication

As any other information in the SmPC, the therapeutic indication is initially proposed by the applicant and will finally reflect the CHMP position on the medicinal product following the assessment of the application.

---

2 Extract from SmPC guideline (Revision 2, September 2009):

"4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

Study endpoints should not normally be included, unless such mention is specified as being appropriate for the indication in CHMP Guidelines. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

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.

Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.
If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication."

The assessment of the indication should take into account:

- The data submitted as part of the application (i.e. the population actually studied in clinical trials and also the understanding of modifiers of the pharmacokinetic (PK) profile, pharmacokinetic/pharmacodynamic (PK/PD) relationship, etc.);

- the therapeutic context (e.g. current therapy recommendations, rational supporting previously approved indications);

- whether the benefits and risks in the studied population are applicable to the proposed target population.

Therefore, defining the therapeutic indication requires a multidimensional analysis of aspects that influence the benefit/risk assessment.

To facilitate a consistent approach when deciding on the wording of the therapeutic indication, different components have been identified to be considered when defining the therapeutic indication. These components may be more or less relevant depending on the medicinal product and the target population, but will be applicable to medicinal products in most therapeutic areas. For some medicinal products, other components may be of importance which are not covered by this guide. The exact wording of the indication, therefore, remains a case-by-case decision.

Following the assessment, the final wording of the indication may be wider or more restricted compared to the therapeutic indication as initially proposed by the applicant as well as compared to the population studied. **The scientific basis for and the reasoning behind the final wording of the indication should be clearly documented in the CHMP assessment report, namely the benefit/risk section**. In particular, if an established positive benefit/risk balance in the studied population is extrapolated to subgroups for which data are scarce or absent (i.e. the indication will be broader than the study population), this should be clearly justified. This is equally important if the target population identified by the indication is more restricted compared to the study population.

The following components can be applied to most therapeutic areas when deciding on the wording of the indication.

1) Target disease or condition

- The indication should **define the target disease/condition** in a way that is well recognised in clinical practice.

- The **effect of the medicinal product**; treatment, prevention or diagnostic; should be defined (as specified in the SmPC guideline).

  – Treatment can be specified as symptomatic, curative or modifying the evolution or progression of the disease (or condition) and it should be considered if specifying this in 4.1 is important to the prescriber.

    Example; it can be of relevance to specify "symptomatic treatment" or treatment of a certain symptom if this is the only effect of the treatment. On the other hand, a claim of effect on evolution/progression (e.g. "disease modifying treatment") should only be granted if clear criteria for such an effect exist and is of relevance for the prescriber.

- In the case of a **prevention indication**, the condition(s) that is prevented should be specified as well as, if applicable, whether the aim of the prevention is primary or secondary prevention.

- Information on **duration** of treatment should, in general, be included in section 4.2, and should not be mentioned in 4.1.

    – Example; avoid inclusion of wordings like "long term treatment" since it is often difficult to define what study duration would be needed to support such a claim.

- **References to study endpoints** should, in general, not be included in 4.1, but may be included in 5.1 (see SmPC guideline for further guidance for section 5.1).

    – In rare cases, a product may not be aimed for treatment of the disease/condition as such, but to alleviate a certain symptom. In that case, endpoint(s) may be included in 4.1 (example; *X is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability*).

- Has only a **specific type** of the disease/condition been studied (e.g. relapsing remitting multiple sclerosis or a certain type of epilepsy, disease due to a particular microbe)? If yes, consider restricting the indication to this type unless the benefit/risk balance can be extrapolated to other types of the disease/condition (see further below concerning extrapolation principles).

2) Target population

- The target population should be **well defined** and recognised in clinical practice;

- **It is crucial to consider whether the benefit/risk balance is positive or not in relevant subgroups** of the target population since this may influence the wording of the indication;

    – Define relevant subgroups of the target population experiencing the disease/condition in clinical practice (based on, e.g. age, gender, certain severity stages of the disease, organ function impairment, pharmacogenomics variants).

- Often, there may be very limited data for some of the subgroups or they may not have been studied at all. The following aspects should be considered when assessing the benefit/risk balance for a subgroup with limited data;

    – Consider why the data is limited/absent for a certain subgroup (e.g. based on epidemiology, exclusion criteria or recruitment problems);

    – In case there is some available data in the subgroup, the assessment report should discuss if results are consistent with results in the total study population (e.g. by considering the point estimate and its precision). Consider also the extent to which a consistent (or inconsistent) effect has *a priori* plausibility (see CHMP guideline on the investigation of subgroups in confirmatory clinical trials);

    – If required, can the conclusions drawn in the total study population be extrapolated to the subgroup in question?

    This evaluation should be based on different sources of knowledge, e.g. about the disease (differences in clinical or demographic characteristics or pathophysiology in different subgroups), the drug class (mechanism of action), PK/PD modelling, population pharmacokinetic analysis (Pop-PK).

The table below illustrates possible results of such evaluations with respect to wordings in the SmPC:

Assessment of benefit/risk balance in relevant subgroups not studied or with limited data	Wording in the SmPC
Benefit/risk balance positive Available data support that efficacy/safety in the subgroup is consistent with study population and/or efficacy/safety in study population can be extrapolated to the subgroup.	No need to restrict the indication (4.1) with regard to the subgroup, e.g. with upper age limit, severity stage, gender etc. Consider reflecting any limitation of data in certain subgroups in the SmPC 4.2 and/or 4.4, e.g. "*data in patients above the age of 65 years is limited*"
Benefit/risk negative based on lack of efficacy Effect is considered to be absent/very low in a subgroup based on the available data and/or previous knowledge. The efficacy results in the study population cannot be extrapolated to the subgroup in question.	Include restriction (e.g. age limit, disease severity) in the indication (4.1).
Benefit/risk negative based on safety issue Based on available safety data	Include contraindication (4.3) for the subgroup (e.g. severe renal impairment).

3) Place in therapy (e.g. first line, second line)

The following aspects should be considered;

- Consider **if there is a defined treatment pathway** in the condition studied; are treatments defined as first and later line treatment? If this is the case, in which population/part of the pathway has the medicine been studied?

- Can the conclusions on the benefit-risk balance be extrapolated beyond the line of treatment which has been studied such that the benefit/risk is positive for a broader use?

- If the data can be extrapolated to other lines of treatment or if the medicinal product has been studied in both first and later lines, it may not be necessary to specify "first line" or "second line" in 4.1.

- If the product has been studied in a first line setting, but data is not considered to support a first line indication, restrictions to second/third line treatment or to patients with contraindications or intolerance to first line standard of care could be considered if therapeutic efficacy and the benefit/risk balance are established to be positive in that population (e.g. if a more relevant benefit is established in patients with a later stage of the disease who have fewer treatment alternatives).

- If the product is studied in a second/third line setting, consider if there is a need to specify previous treatments to which patients are non-responders or intolerant

  - This may be relevant if it is expected that the sequencing of specific previous treatments might impact the efficacy or safety of the new therapy;

  - If this is not the case, it could be sufficient to use expressions like "candidates for systemic therapy" or "non-responders to conventional therapy" instead of specifying previous treatments. **The interpretation of such expressions should be explained in the assessment report.**

4) Use in monotherapy/ combination therapy

The need to specify in SmPC section 4.1 if the product should be used as monotherapy and/or in combination with other products will depend on the design of the studies supporting the application as well as an assessment if the benefit/risk balance for regimen(s) studied can be extrapolated to those not studied. Any extrapolation should be discussed and justified in the assessment report.

Monotherapy

Consider specifying "monotherapy" in 4.1 if this is the way the product has been studied and use in combinations with other products will result in a negative benefit/risk balance due to safety concerns or uncertainties with respect to the efficacy in combination therapy.

Combination therapy

If the product has been studied in combination with other products, this should be considered to be specified in SmPC section 4.1, if the benefit/risk balance is positive only in this setting.

In any case, information on drug interactions should be presented in SmPC section 4.5 and, possibly, in section 4.3 or 4.4.

- If there is a need to specify use in combination therapy in SmPC section 4.1:

Is there a need to specify particular combinations (e.g. the studied combinations if it is expected that the benefit risk balance may differ with other combinations) or could a general statement ("*in combination with other products*") be used (with information on combinations studied reflected in other parts of the SmPC)? If so, since the description of performed studies in section 5.1 cannot be seen as restricting or broadening the indication, restriction or extrapolation in section 4.1 in terms of combination therapy should be justified in the assessment report.

5) Mandatory condition of product usage

Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may also be included (e.g. concomitant dietary measures, lifestyle changes or specific screening modalities).

IV. The final wording of the indication

When all these components have been considered, some or all of the items in the following mock-up may be relevant to cover in the indication statement:

Template wording of therapeutic indication

<Diagnostic use >or <Preventive> or <Symptomatic, curative or disease modifying (if applicable)> <treatment of> <{severity criteria if applicable}> <{target disease or condition}> in <{age group}> patients < {restrictions to patient population, if applicable}> <{restrictions in terms of therapeutic option or prior therapy, or other restrictions, if applicable}> <in combination with other medicinal products <{list relevant combinations, if applicable}><in monotherapy>

<{Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC}>