EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need to revise the "Guideline on the evaluation of anticancer medicinal products in man" in order to provide guidance on the reporting of safety data from clinical trials

Draft

Draft agreed by ONCWP	16 February 2015
Adopted by CHMP for release for consultation	26 February 2015
Start of public consultation	1 May 2015
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Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	*Cancer, malignancy, lymphoma, leukaemia, safety data, AE, SAE, reporting*

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1. Introduction

The shift from conventional cytotoxic drugs to so called targeted drugs and immune modulators administered continuously and at maximum tolerated dose has changed the tolerability and toxicity profiles of anti-cancer drugs. Among medicinal products, however, anti-cancer drugs still stand out compared with other therapeutic areas.

2. Problem statement

Currently, safety data in clinical trials are mainly collected and presented in a cumulated and therefore not sufficiently differentiated fashion. However, the incidence, prevalence and severity of certain AEs change over time, particularly in oncology. Furthermore, it is uncertain to what extent dose reductions alleviate the event(s) leading to dose reduction in the first place. Another problem is our current inability to make fair comparisons of ADR frequencies between products, due to differences in treatment length across studies. In that respect, add-on designs are a particular challenge. Furthermore, in oncology it is often difficult to assess causality of adverse events in relation to the investigational drug due overlapping symptoms of the underlying malignant disease and toxicity from other backbone therapies. Therefore, complementary ways to present safety data are warranted.

3. Discussion (on the problem statement)

The aim of this revision is to find ways on how to report AEs in order to improve the understanding of the toxicity and tolerability profiles of medicinal products. This could include: incidence and prevalence per period of time, time to event, time-adjusted analyses for AEs (e.g. by different cut-off dates or event rates per 100 patient-years) if justified based on the event rate profiles over time. It is not anticipated that all AEs would need to be reported in such detail, however. Selection criteria could for example include events leading to dose reduction or interruption, SAEs, events that are likely to affect tolerability and events of special interest, e.g. based on pre-clinical data.

Another issue may be to what extent dose reductions actually alleviate the event(s) leading to dose reduction. Evaluation of longitudinal PK/PD-data, where dose adjustments are taken into account, may provide further insights.

For studies in the paediatric population, adverse events should include the reporting of effects related to organ maturation and long term effects on growth and development, but it also appears important to see if younger children have more toxicities and how toxicities accumulate over treatment cycles.

Fully acknowledging the problems of between-study comparisons, the assessment of safety data may be improved if all applications included adverse event rates at specified time points (e.g. 3 months, 6 months and 1 year), which may facilitate comparison across products. This could be particularly useful in the assessment of applications based on single-arm pivotal studies.

4. Recommendation

The Working Party recommends revising the “Guideline on the evaluation of anticancer medicinal products in man” in line with the above discussion. Relevant Working Parties may want to be involved in the review of this guideline revision.

5. Proposed timetable

It is anticipated that a draft updated guideline may be available 6 months after the adoption of the Concept Paper to be later released for 3 months external consultation and, thereafter, finalised within 7 months.

6. Resource requirements for preparation

The update of the guideline will be driven by the Oncology Working Party; it is anticipated that at least two Working Party meetings will be needed. Prior to release, the review will involve the Scientific Advisory Group Oncology.

7. Impact assessment (anticipated)

The aim of updating the guideline is to facilitate discussions within the CHMP and its scientific Committees and Working Parties and to improve the communication of safety data. Moreover, improved safety presentation in the initial submissions of applications, as a result of these expectations being expressed in the guideline, may reduce the number of questions to the applicant.

8. Interested parties

ESMO, EORTC, EFPIA

9. References to literature, guidelines, etc.

Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4).

Draft reflection paper on the use of patient reported outcome (PRO) measures in oncology studies (EMA/CHMP/292464/2014).