EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Scientific and Regulatory Management Department

Summary of Product Characteristics Advisory Group (SmPC AG) 2010-2015 activity report

Quality assurance of SmPCs

1. Introduction

During the public consultation for the second revision of the SmPC guideline in 2008, healthcare professionals supported the principles of the guideline and welcomed any initiative to improve the clarity of the SmPCs to favour daily medical practices. In response to this wish the SmPC Advisory Group was established (in 2010) to promote and facilitate the application of the SmPC guideline. Its main activities consist of trainings, answers to SmPC queries raised by the regulatory network, and, preparation of its annual activity report, considering the impact of the SmPC implementation plan on product information and related regulatory guidance and processes. This fifth report summarises the experience of the group since its creation.

2. SmPC AG activities

Training activities

Over time, training activities have been the core objective of the SmPC AG. They started with the creation of a dedicated webpage providing the regulatory network with information and tools to help reviewing SmPCs in line with the SmPC guideline (EudraSmPC webpage). The website was launched in 2010 with communications to National Competent Authorities, EMA and its scientific committees. Two years later, the SmPC AG launched a new version of the webpage, incorporating Frequently Asked Questions and Videos, as well as a public interface allowing to share training material with pharmaceutical companies. The EudraSmPC webpage has been continuously used within the regulatory network with peaks following its launch and upgrade (See Figure 1). The most consulted documents on the EudraSmPC webpage have switched from the training presentations to the SmPC AG Q&A (see below). Regarding the public interface, the Video “Introduction to the SmPC” presented on top of this public webpage is one of the Top 10 most popular EMA video on YouTube (See Figure 2). Assessors use more the EudraSmPC webpage because its design is more user-friendly, and, allows consultation of past SmPC AG (Q&A).

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Figure 1:

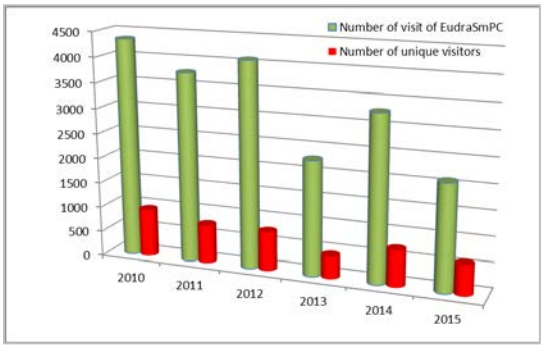
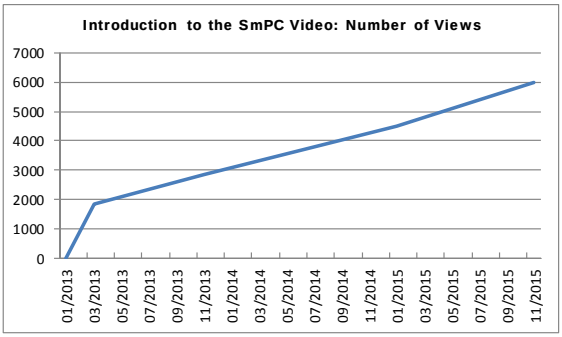


Figure 2:



The SmPC AG has also been organising regular SmPC webinars within the regulatory network since 2011 (5/y). Attendance has been high and growing over years (from about 100 participants to more than 200). Webinars are covering a broad range of information to be communicated in SmPC, reiterate general principles of the SmPC guideline and address areas where difficulties have been identified. Since 2012, each webinar includes an interactive presentation with case studies. The feedback received from the participants is very positive; participants welcome webinars as a very useful training forum within the regulatory network, which also allows sharing experience and building expertise and consistency. Webinars are recorded and made available to the network via the EudraSmPC webpage. SmPC webinars are also advertised on the EU Network Training Centre website, and their attendance is part of continuing professional development in some National Agencies.

Webinars and SmPC webpages are recognised as a cost-effective means of training and reference material.

SmPC AG members have also been regularly invited by Committees and Working Groups/Parties or to external meetings to provide training on product information or discuss related issues.

SmPC queries

SmPC Advisory Group members regularly advise on SmPC-specific queries as part of their core activities, e.g. when supporting scientific committees' or working groups' activities. Many queries are addressed by members individually since they relate to issues which are clearly addressed in the SmPC guideline or have been previously addressed by the SmPC Advisory Group. In addition, the SmPC Advisory Group has prepared about 140 Q&As which have been made available on the EudraSmPC webpage. These Q&As, which initially largely reiterated the general principles of the SmPC guideline, have become more complex in addressing new types of information with limited guidance in the SmPC guideline (e.g. pharmacogenomics information, environmental risk assessment, data in non-approved use, drug interactions, cell therapy, new pharmaceutical forms, comparative data, information borderline with disease management, presentation of information for fixed dose combination). Another factor adding complexity when providing advice relates to the unavoidable uncertainties in the scientific conclusion due to data limitation (e.g. on causality assessment of adverse events, estimation of frequency of adverse reactions, theoretical risks [e.g. based on non-clinical findings, pharmacokinetic investigations or immunogenicity data], clinical relevance of secondary efficacy endpoints, or, definition of the target population of the indication). Even if the latter issues are primarily related to assessment, more guidance on how to communicate in areas of uncertainties would be valuable.

Other support to quality assurance

The SmPC AG has developed a list of scientific guidelines with SmPC-related recommendations which is available on the EudraSmPC webpage and its public interface.

The group also developed a SmPC Guideline checklist in 2012-2013, which has then been posted on the EudraSmPC webpage, and, promoted its use as part of good practice for product information review.

In 2015, the group contributed to the revision of the product information review process for new applications; its aim is to simplify the process by consolidating all comments in a single document, to ensure earlier identification of issues to be addressed, to increase consistency between products and Committees' assessment, and, to optimise the establishment of labeling standards. The new process has been implemented as of May 2015, therefore, more time is necessary before fully assessing its effect. However, initial feedback confirms the expected benefits of strengthening early review and reducing workload, by compiling all reviewers' comments into a single document from the start of the marketing authorisation procedure.

3. Impact of the SmPC implementation plan

According to its mandate, the SmPC AG has established a platform of training, experience-sharing and support for specific issues raised during the evaluation process. For example, SmPC webinars are well-recognised as training tools for new assessors as well as part of their continuous education. When providing training, it is continuously stressed that SmPC review is an integral part and a primary objective of assessment to ensure that information is evidence-based, useful in clinical practice and consistent with other regulatory information, such as the risk management plan. It is also the opportunity to stress the need for keeping information updated throughout the life-cycle of the medicines, including in specific areas such as pregnancy and lactation. The group also contributed in reinforcing the quality assurance system with the creation of a SmPC checklist and the revision of the product information process.

Implementation of the 2009 recommendations for improving SmPC paediatric information has been successful. Progress has also been made regarding information on other subpopulations (e.g. elderly or pharmacogenomics subpopulation), which could be consolidated by expanding guidance to further standardise related information in SmPC. As information should be data-driven, the SmPC AG welcomes the recent initiative to pilot a revision of the CHMP assessment report template to improve clarity of geriatrics-specific issues; this is an important step to consider whether information in elderly is sufficiently addressed in the SmPC, e.g. in reflecting potential gaps in the development programme relating to older subjects. The group also noted a growing demand for investigating potential gender differences.

Similarly, the structure of section 4.8 has improved in terms of compliance with the revised (post-2009) guidance, e.g. inclusion of a single tabulated list of adverse reactions independently of the source of information (e.g. clinical trial or post-marketing). The recommendation for a summary of safety profile (and not a summary of the safety database) as an introduction to section 4.8 has been reinforced with the new product information review process, and is expected to promote clearer information on undesirable effects in the PL. Assessment related issues (e.g. strength of causal relationship or estimation of frequency) remain sometimes a challenge (e.g. when adverse reactions are also observed in the natural course of the disease or with products used in combination or identified through spontaneous reports). The description of selected adverse reactions may help to address such challenges, but it may also become lengthy, too factual, or, overlapping with information in section 4.4.

Redundancies and overlapping of information between section 4.4 with section 4.8, but also with other sections such as 4.2, 4.5, 4.6, may hamper readability of SmPC, and represent an area for improvement.

In terms of efficacy information, efforts were made to prevent inclusion of information (e.g. in section 5.1) which could be seen as constituting a different indication than the one presented in 4.1. The CHMP, in close collaboration with SmPC AG representatives, has recently initiated a reflection paper to develop guidance on the wording of the therapeutic indication that can be applied across therapeutic areas. The SmPC AG has regularly warned on the growing amount of information in section 5 which may hamper extraction of the most relevant information. It is acknowledged that the extent of information to communicate is a matter of a case by case assessment in selecting information relevant to the prescriber. However, it is recognised that the SmPC guideline does not provide detailed guidance on which information to present under the subsections "mechanism of action" and "pharmacodynamic effects". It has also been seen that some information (e.g. subgroup analyses) is frequently included although not foreseen in the SmPC guideline.

The SmPC Advisory Group had also initiated a reflection on off-label use and SmPC information, which has supported committees' discussion when facing off-label use issues. Following EC's initiative to carry out a study on off-label use, the work has been temporarily put on hold.

In its second activity report the SmPC AG recommended to give due attention to the report on shortcomings of readability of SmPC and PL to be prepared by the European Commission according to the 2010 Pharmacovigilance legislation. Based on the current feedback, the quality of SmPC has been assessed as reasonable, even if some suggested areas for improvement regarding clinical pharmacology information, drug interactions, undesirable effects, and, facilitation of extraction of significant information.

4. Discussion and recommendations

SmPC information has a dual objective. The SmPC is the most important information validated by competent authorities to provide healthcare professionals (and public through the PL) with patient-oriented, evidence-based, reliable and up to date information on authorised medicines. The SmPC is also a regulatory document with legal implications, e.g. in terms of conditions for use (vs "off-label use"), communication of safety information, or, advertising to healthcare professionals.

The high level structure of the SmPC, defined in Directive 2001/83/EC, is well-established for all authorised medicines throughout EU. Since 1999, the EC SmPC guideline provides advice on the principles of presenting information in the SmPC. It was revised in 2005 and 2009 mainly to clarify recommendations on therapeutic indication, and, paediatric and safety information, respectively. The primary objective of the SmPC guideline did not change, i.e. to ensure that SmPCs provide clear and concise information for healthcare professionals on how to use the medicinal products safely and effectively. However, the framework for preparation and use of SmPC has gradually evolved. For example, in terms of SmPC content, users' demand for information has increased (e.g. for individualised therapy, or, more transparency), and, scientific development (e.g. investigation of drug interaction, pharmacogenomics, companion diagnostic, advanced therapy medicinal products, novel administration devices, knowledge on diseases, …) and regulatory scrutiny of available evidence (e.g. in subpopulations or on safety) is continuously progressing. In terms of use, changes in healthcare practice stemming, for example, from Health Technology Assessment or IT development may have changed the way SmPC is used. The EMA/CHMP/PRAC Healthcare Professional Working Party has

engaged in a project to prepare recommendations on how to maintain high quality of product information throughout the lifecycle to support clinical practice. Together with the final EC report on SmPC and PL, this project may help to identify potential areas for improvement according to healthcare professionals' needs.

Current feedback shows that the overall quality of SmPC is satisfactory; however, continuous effort is necessary to ensure that it consistently achieves its objectives and addresses new demand for information or scientific progress. The increasing amount of information to be communicated may hamper users' ability to target the information they need, not only for some new medicines, but also for some older ones, which need to be updated throughout the life-cycle of the medicine. With increasing length and complexity of the SmPC, the needs of the prescriber have to be considered, to ensure optimal presentation to make it easy to find the most important data.

The SmPC AG therefore proposes:

- to continue promoting the application of the SmPC guideline through its current activities (including monitoring of potential deviation from the principles of the guideline, and, development of Q&As as tool for further substantiating its principles),
- to consider and act on the recommendations of the upcoming Commission report on "Shortcomings in the SmPCs and the package leaflet,
- to investigate whether defining further standard subsections (e.g. in 4.4 or 5.1) could help improving readability of lengthy SmPC,
- to compile new or pending SmPC issues (e.g. regarding immunogenicity or Pharmacogenomic), for which FAQs could be prepared in cooperation with concerned working party, when sufficient experience has been gained,
- To promote optimal presentation of data, maintaining a balance between inclusion of all relevant information with exclusion of reduntant information especially if this information can be presented elsewhere.
- To follow any evolution in HCPs' needs and use of information on medicines that would impact on SmPC.

Suitable human and technical resources should be ensured for putting in place those recommendations.