Guidance for Type II variations involving revision of the SPC sections 4.6, 5.3 and 6.6

Introduction

Taking into account the recurrent similar remarks that have been formulated with respect to Type II variation applications involving revision of the SPC sections 4.6 and 5.3 over the past months, more detailed guidance is now provided on the non-clinical dossier requirements and on the formulation of the SPC sections 4.6, 5.3 and 6.6 and the PIL (environmental risk assessment).

The application of this guidance is expected to avoid future delays in the granting of approval for type II variation involving updates of the above mentioned sections of the SPC.

Dossier requirements

The Notice To Applicants Volume 2B states the following for variation applications in accordance with Regulation 1084/2003/EC and Regulation 1085/2003/EC (excerpt of the NTA Vol.2B):

> Type II Variation Applications and their supportive documentation – where appropriate – should be presented as follows (non-exhaustive list depending on the scope of the variation and supportive data):
>
> Module 2:
> As mentioned in the Variation Regulation any Type II variation should be accompanied by the relevant Overviews/Summaries updates or addenda (even if a variation is submitted at the request of the Competent Authority/CHMP). Expert details and signature are to be provided in Module 1.4 separated from the actual Overview/Summary.
>
> Module 3, 4, 5:
> Supportive data are to be included in Modules 3, 4 and/or 5 as appropriate and in accordance with the EU-CTD structure.

Consequently, for Type II variations involving modifications of the SPC pertaining to the non-clinical data a non-clinical overview conform the requirements set out in Annex I to Directive 2001/83/EC as amended, should be submitted in Module 2 with supportive data included in Module 4.

This is especially important when:

- New non-clinical data are introduced
- Non-clinical data are reported in section 5.3 which formerly was indicated as “not applicable”.

SPC

Section 4.6 Fertility, pregnancy and lactation

This section should be formulated taking into account the recommendations made in:

- the EMA Guideline on Risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/2005; July 2008), and

data to labelling

- the revised Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice to Applicants, September 2009).

SmPC Guideline

More specifically, the Guideline on Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice to Applicants, September 2009) states the following (excerpts from the guideline):

In case of contraindication, this should be included in section 4.3.

Women of childbearing potential / Contraception in males and females
Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test or contraceptive measures. Where an effective contraception is required for patients or partners of patients during treatment or for a defined period before starting or after ending treatment, the rationale should be included in this section. If contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

Pregnancy
In general, clinical and non-clinical data should be followed by recommendations.
With respect to non-clinical data,

- only conclusions of the reproductive toxicity studies should be included in this section. Further details should be provided in section 5.3.

With respect to clinical data,

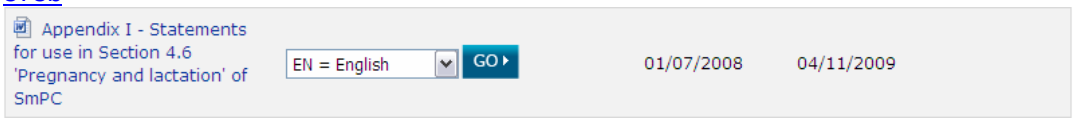
- the section should include comprehensive information on relevant adverse events reported in the embryo, the fetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) should be specified when available.
- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy.

With respect to the recommendations:

a) Recommendations on the use of the medicinal product during the different periods of gestation, including the reason(s) for these recommendations, should be given.
b) Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as fetal ultrasound, specific biological or clinical surveillance of the fetus or the neonate) should be given.

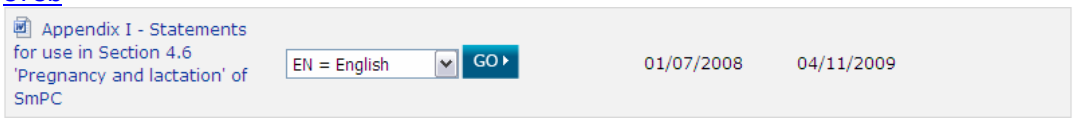
Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

The example statements with respect to pregnancy as included in the EMA Guideline on Risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/2005; July 2008) should also be used. For example statements in all national languages see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000267.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800b378b



Breastfeeding
If available, clinical data should be mentioned (exposed breastfed infants) as the conclusions of kinetic studies (plasma concentrations in breastfed infants, transfer of the active substance and/or its metabolite(s) into human milk…). Information on adverse reactions in nursing neonates should be included if available.
Conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.
Recommendations should be given to stop or continue breastfeeding and/or to stop or continue the treatment in cases where treatment or breastfeeding discontinuation is recommended, and the reason should be provided.

The example statements with respect to lactation as included in the EMA Guideline on Risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/2005; July 2008) should also be used. For example statements in all national languages see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000267.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800b378b



Fertility
The main information on the possible effects of the medicinal product on male and female fertility should be included in section 4.6.
This section should include:
a) Clinical data if available.
b) Relevant conclusions from nonclinical toxicity studies, if available. Further details should be included in section 5.3.
c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.
Cross-references could be included in section 4.3, if appropriate.
If there are no fertility data at all, then this should be clearly stated.

Section 5.3 Preclinical safety data

This section should be formulated according to the recommendations of the revised Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice to Applicants, September 2009).

More specifically, the Guideline on Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice to Applicants, September 2009) states the following (excerpts from the guideline):

Information should be given on any findings in the non-clinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorized indication(s), and which is not already included in other relevant sections of the SmPC.
If the results of the non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SmPC.
The findings of the non-clinical testing should be described in brief with qualitative statements as outlined in the following example:

- *Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.*
- *Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.*
- *Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: ….*

Findings of non-clinical studies relevant for use in the paediatric population, including juvenile animals and peri- or post- natal studies, should be presented with a discussion of their clinical relevance, under a sub-heading if necessary.

<Environmental Risk Assessment (ERA)>
Where relevant, conclusions on the environmental risk assessment of the product should be included, with reference to section 6.6.

Reporting on environmental risk assessment: SPC Section 6.6 and PIL

SPC Section 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The part of this section related to the environmental risk assessment should be formulated taking into account the recommendations made in:

- Guideline on the environmental risk assessment of medicinal product for human use


ERA

(EMEA/CHMP/SWP/4447/00) , and
- the revised Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice


SmPC Guideline

to Applicants, September 2009).

More specifically, the Guideline on Guideline on summary of product characteristics (SmPC) (EU Volume 2C Notice to Applicants, September 2009) states the following (excerpts from the guideline):

Instructions for disposal should be included here, if appropriate for the product.

Where special precautions for the handling and disposal of certain products such as cytotoxics and some biological products or waste material derived from it are advised, e.g. in the case of products containing live organisms, these should be stated in this section, as should, where relevant, the disposal of items which come into contact with the product, such as nappies, or spoons used to administer oral vaccines. If relevant, a cross-reference to conclusions on the environmental risk assessment described in section 5.3 can be included.
If applicable, e.g. for cytotoxics, the following standard statement should be included, *'Any unused product or waste material should be disposed of in accordance with local requirements.'*

If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the standard statement, *'No special requirements.'* should be included.

In case of contraindication, this should be included in section 4.3.

PIL

With respect to the PIL, the Guideline on Guideline on the environmental risk assessment of medicinal product for human use (EMEA/CHMP/SWP/4447/00) states the following (excerpts from the guideline)

In order to enhance environmental protection, it is recommended that – even for medicinal products that do not require special disposal and, measures - package leaflets (patient information leaflets) should include the following general statement:
"Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment."

Additional labelling should be employed only when warranted (e.g. radioactive isotope preparations or medicines concentrated in devices) in which circumstances the measures to be taken should be practical and realistic given the anticipated use of the product.