pharmiceutics LLC

To:

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European Commission
Enterprise and Industry
Directorate-General

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Public consultation on the proposed "Strategy to Better Protect Public Health by Strengthening and Rationalizing EU Pharmacovigilance"

Pharmiceutics LLC is a Pennsylvania-based company specialized in consulting and training in the area of Core, EU and US medicines labeling and related regulatory aspects.

Our comments on the labeling elements of the proposed strategy:

1. Proposal to add a new section to the SmPC to highlight key safety information and how to minimize risks

Instead of adding a new section, the Commission should take steps to ensure a more effective use of the existing section 4.4, Special warnings and precautions for use.

Background:

Section 4.4, when populated based on the information provided in the SmPC guideline (including the December 2007 draft guideline), covers a broad range of safety related information, including:

- warnings about serious risks (possibly accompanied by advice to consider avoiding the product ["relative contraindications"])
- information on population subsets with unique risks (even if not serious)
- information on population subsets with increased risk (in terms of the nature of reactions and/or frequency)
- advice to take precautionary measures

Frequently, statements about the lack of information on safety and effectiveness in a specific subpopulation are found included in this section, if placing them in other sections, such as 4.2 or 4.6, is not considered appropriate.

If not well organized, the mixed content of the *Special warnings and precautions for use* section might make the section difficult to use in the following important clinical situations:

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Situation A: Selecting the best product for a specific patient

Question: Is there any special information regarding the characteristics of the "patient in front of me"?

In this situation a break down of information per subpopulation is helpful.

Situation B: Need to learn about the risks of a product

Question: What is known about the risks of this product? Need information that that helps me diagnose and/or manage a suspected adverse reaction.

In this situation a break down of information per risk is helpful.

Our proposals:

- ***To accommodate the different "search patterns" of healthcare professionals, the information in section 4.4 should be sub-structured as follows:***

  First group of information in 4.4: ***Special warnings, with or without advice to consider avoidance***

  "Special Warnings" should NOT be a subsection title.

  Presentation of important risks, in order of decreasing importance. Presented as formal subsections (3rd level subsections) with a subsection title that identifies the risk (e.g. "Severe infusion reactions", "Myelosuppression").

  The risks presented here can include warning-worthy risks resulting from drug interactions, and risks that are anchored in other sections of the SmPC.

  For each risks, the subsection should briefly refer to subpopulation-specific information provided in the second group of information, if applicable (see below).

  Where appropriate, this first part of section 4.4 can list/summarize and explain precautionary measures that apply to all patients/consumers (not only to specific subpopulations).

  Second group of information in 4.4: ***Specific Populations***

  "Specific populations" should be a 3rd level subsection title. This subsection should be omitted when there is no pertinent information.

  This section would house further (4th level) subsections, including a pediatric population subsection and subsections for any other relevant population subsets such as patients with renal impairment.

  The information provided for each subpopulation should address unique risks and increased risks, as well as any safety precautions and other relevant information.

  This section should also contain statements about the lack of information on safety and effectiveness in a specific population, if the statement is intended to discourage use in the population based on a suspected unfavorable benefit/risk balance.

If such a statement is intended to be a mere "statement of fact" and not intended to discourage use, it should be included in section 4.8 and/or 5.1, as appropriate. Statements intended to formally restrict the indication should be provided in section 4.1 in the context of the delineation of the target population for use.

This subsection (*Specific Populations*) should also include mandatory cross-references to sections 4.6 and 4.7.

The principles for populating this subsection (*Specific Populations*) would be similar to the principles for populating the *Use in Specific Populations* section in new-format US labeling, with the exception that the *Specific Populations* subsection of 4.4 would focus only on safety information and on unknown, borderline or negative benefit/risk balance, and not also provide a summary of effectiveness and other information.

. Third group of information in 4.4: ***Warnings and precautions for persons handling <product>***

"Warnings and precautions for persons handling <product>" or something similar should be a 3rd level subsection title. This subsection should be omitted when there is no pertinent information.

This way of organizing the content of section 4.4 inevitably leads to a certain level of duplication of information between group 1 and 2. However, some degree of duplication is beneficial for presenting information so that its structure accommodates the different needs of healthcare professionals.

The new US labeling format, with its *Warnings and Precautions* section (largely equivalent to proposed group 1) and *Use in Specific Populations* (comparable to group 2) shows that labeling can accommodate the different "search patterns" of healthcare professionals without excessive duplication of information, provided that the principles of good paragraphing are followed.

- ***If necessary, information of outstanding importance can be highlighted by bold print or by placing it in a "black box".***
  A black box (to make it a section-neutral tool for presenting risks, contraindications or other information) should be located at the top of the SmPC and not within section 4.4.

  Highlighting information by bold print and a box is already possible now.

- ***The SmPC guideline should provide a better/clearer definition of the threshold for including information in section 4.4 and its subsections.***

  For the first group of information in 4.4 (list of risks) the *relevance* threshold should be
  - "serious in a general sense" (i.e. NOT based on the regulatory definition of seriousness) or,
  - "serious or otherwise clinically significant" (serious in a general sense or based on the regulatory definition; otherwise clinically significant defined by typical examples [see also draft FDA guidance]).

  The "serious or otherwise clinically significant" threshold has been chosen for the US *Warnings and Precautions* section.

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. For the proposed *Specific Populations* subsection of 4.4 the *relevance* threshold should be
- "serious or otherwise clinically significant" (see above) or simply
- "undesirable" (which is the relevance threshold for items included in the Undesirable Effects section, 4.8).

The latter threshold would lead to inclusion of all adverse reactions (ADRs for the purposes of labeling) with increased frequency or seriousness in a subpopulation, even if the adverse reaction as such is not clinically significant; this would cause a significant degree of duplicate information between section 4.4 and section 4.8, unless the rules for populating 4.8 are changed (to avoid or reduce discussion of subpopulation-specific differences in the nature or frequency of adverse reactions).

We propose that the *certainty* threshold for 4.4 (i.e. how sure we have to be that a causal association is "real") is the same as for section 4.8, i.e. "reasonable suspicion" or "reasonable possibility" of causal association.

An important advantage of a better defined and more disciplined approach to populating section 4.4 is that all of the improvements to this section can be implemented immediately - without any waiting or transition period.

2. Proposal to add a new boxed section to the Package Leaflet to highlight key safety information and how to minimize risks

We agree with the proposal to better identify key safety information and advice on how to minimize risks.
However, this should be done in a way that does not create unnecessary duplication of information and complexity, and makes the leaflet more difficult to navigate and understand.

Background:

In this context, two of the main weaknesses of the current leaflet template is are:

1. The section heading "BEFORE YOU <TAKE> <USE> X" (leaflet section 2)

   The content under this heading corresponds to the content of sections 4.3 to 4.7 of the SmPC.

   Under this heading, the leaflet presents information that is important to consider both
   - *before use* (to verify consent to treatment) and
   - *during use* (in case of a new issue, such as an emerging contraindication).

   By contrast, the heading "BEFORE YOU <TAKE> <USE> X" de-emphasizes the need to study the content of "POSSIBLE SIDE EFFECTS" before use.

   Verification of the acceptability of even "minor" adverse reactions that are NOT elevated to a more prominent place is an important part of selecting medicines. There will always be adverse reactions that are not considered warning-worthy by the authors of labeling, but considered prohibitive by an individual patient (such as changes in voice for a singer).

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2. The subheading "Take special care with X" of leaflet section 2

   This subheading (at least in its English version) is not a good subheading for the range of information presented in the SmPC's section *4.4, Special warnings and precautions for use* (which was, to our knowledge, the original scope of this leaflet section).

   While the subheading is appropriate for, e.g., information about subpopulations with special risks or benefit/risk issues (see discussion of the second group of information on the SmPC's section 4.4, above), many readers do not expect to find a list of important risks in this section, if at all included.

Our proposals:

To increase the visibility of important safety information and advice on risk minimization, we propose the following changes to the package leaflet template and structure:

A. Either eliminate the section heading "BEFORE YOU <TAKE> <USE> X" or replace it by a heading that
   - does not de-emphasize the importance of reviewing the *Possible Side Effects* section before use, and
   - conveys that the information listed in section 2 of the leaflet is also important during and, possibly, after use.

B. Change the heading "Take special care with X" to better convey that the reader should expect in this section not only safety precautions but also information about important risks (presented in per-risk short paragraphs describing the risks and related precautionary measures).

   However, this section should not repeat *specific* information about specialist-performed interventions in case of an adverse reaction, as it may be provided for healthcare professionals in section 4.4. of the SmPC. Advice regarding *specialist-performed* interventions would, anyway, typically be translated for patient labeling into "clinical-setting precautions" (e.g., "product must be to be administered by under close observation by a physician …).
   On the other hand, this section should contain advice for patients/consumers who suspect experiencing a reaction that is listed in this section; we consider the resulting duplication of advice between this section and the *Possible Side Effects* section acceptable.

C. For products with outstanding safety or benefit/risk concerns, use a "black box-type approach".

   We suggest that the Commission consult with experts in the field of risk labeling for patients/consumers to determine if
   - this information of outstanding importance is better presented at the top of the leaflet, or within the leaflet structure,
   - the use of a box or different means of highlighting is better suited to draw attention to the information.

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In any case, the information that is highlighted by prominent placement and/or formatting should be limited to the one or two issues of outstanding importance, to avoid creating an additional level of safety information that has significant overlap with the content of other sections and thereby increases the complexity of the leaflet and may reduce navigability and clarity.

D. Improve the usefulness of the *Possible Side Effects* section.

The side effects section should be organized to accommodate two typical situations in which it is accessed by a patient/consumer:

1. Review of the list of risks associated with use in order to decide whether or not the benefits and risks are acceptable for the individual user.

2. Searching for information to confirm or refute that a suspected adverse reaction might be caused by the product, and for information on how to act.

For situation 1, a listing/table of adverse reactions sorted by SOCs (SOCs that are meaningful for patients!) and frequency is usually appropriate.
The frequency categories chosen should reflect the best "frequency forecast" by the marketing authorization holder and the agency, and - where there is a relevant background event rate - not be simplistically based on the rate with product while ignoring the background rate.

To accommodate the patients/consumers needs in situation 2, the *Possible Side Effects* section should provide, in addition to the above, a SOC-ordered list of (groups of) reactions and, where appropriate, symptoms of reactions with recommended actions.

Depending on the number and type of adverse reactions, it might be impossible to serve readers in both situations well without subdividing the *Possible Side Effects* section into two parts, with each part optimized for its intended use. Authors of labeling should be encouraged to consider such a subdivision.

Authors of package leaflets should also be reminded that is frequently not possible to provide, in a package leaflet, meaningful and safe advice on necessary actions that holds true for every affected patient/consumer.

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