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| **Submission of EFPIA comments on Public consultation on Excipients in the labeling and package leaflet of medicinal products for human use** |
| **Author: EFPIA** star.png **Date: 22-05-2017** star.png **Version: FINAL** |

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1. General comments

| Comment no | General comment (if any) | Outcome (if applicable) |
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|  | EFPIA welcomes the opportunity to comment on the Draft guideline on Excipients in the labelling and package leaflet of medicinal products for human use. Since the Annex was not included in the review, we conclude that the annex will not be a subject to change compared to the 2003 Annex. |  |
|  | Related to excipients information in the package leaflets:*“The text of this information, written in clear and understandable terms for the patient, should be applied to the package leaflet by default. In some cases the applicant may adapt the style of the information if adequately justified (e.g. by means of user testing) as long as the information content and its meaning remain unchanged.”*Comment:EFPIA acknowledges and strongly supports the importance to ensure that the wording in the annex is patient-friendly as well as the maintenance of this patient-friendliness for subsequent translations. Also the possibility to deviate is welcomed – especially if there is no special consultation of the annex for patient-friendliness (e.g. user testing and other methods of patient consultation should allow changing wording).The text of the annex should be user tested or discussed with patient focus groups or patient representatives. In particular, input of patient representatives should be sought if special conditions are concerned. General EMA consultations do not reach these groups, they should be contacted directly. |  |
|  | Related to specific populations:Comment:Although the [Excipients Drafting Group](http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000127.jsp&mid=WC0b01ac0580a02de1) revised excipients for the Annex to reflect more caution and warning for paediatrics and pregnant women, it might be useful to point to these at-risk populations in the guideline directly with a general statement. We suggest including the older people as well. Proposed change: Under “Excipients in the labelling”, second paragraph, after the first sentence:Please add “information facilitates the safety of special populations such as children, the unborn child, and older people”. |  |

1. Specific comments on text

| Line number(s)  | Comment and rationale; proposed changes*(If changes to the wording are suggested, they are highlighted)* | Outcome (if applicable) |
| --- | --- | --- |
|  | *Introduction:**This is a Commission guideline pursuant to Article 65(e) of Directive 2001/83/EC1. It contains warning statements relating to the presence of certain excipients in medicinal products.*”Comment:The current excipients table lists the labeling statements to be included in the SmPC and PIL depending on certain thresholds.If an excipient is present and below the threshold the statement is still included in the warning section. This could lead to confusion or anxiety for a patient trying to avoid specific excipients.The presence of the excipient and the threshold should be mentioned in the excipient section of the SmPC and should only be included in the warnings if above the designated threshold.Proposed change:It contains warning statements relating to the presence of certain excipients above a threshold in medicinal products. |  |
|  | *Introduction:**Therefore, consistent information should be stated in both documents for all excipients listed in the Annex to this guideline.*The last sentence of the introduction adds a requirement that SmPC and leaflet information has to be aligned. As leaflet information is dictated by the Annex, this has direct effect on the SmPC. However, the SmPC guideline does not refer to the excipient guideline in warning sections (4.4 to 4.6 of SmPC). |  |
|  | *Nomenclature**The following applies to the names of all excipients on the labelling, package leaflet and the SmPC.*”Comment:* Instead of stating as labelling this could be specified clearly, recommendation below if labelling refers to packaging component.
* To reduce agency queries, we suggest adding the following information after the first sentence: *Names should be aligned with 3.2.P.1 and 2.6 of the marketing application where possible*.

Proposed change:“The following applies to the names of all excipients on the labelling (outer package, or if no outer package, then on the immediate package), package leaflet and the SmPC. Names should be aligned with 3.2.P.1 and 2.6 of the marketing application where possible*.*” |  |
|  | *Nomenclature**Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations and/or latin names for excipients may appear on the labelling, on condition that the full name of the excipients in the national language appears in the SmPC and the package leaflet.*Comment: Please consider adding a column with acceptable abbreviations to the Annex. For example the use of abbreviations on small containers is welcomed from a practical point of view |  |
|  | *Nomenclature**Excipients should be referred to by their recommended international nonproprietary name (INN or INNM) accompanied by the salt if relevant, or the European Pharmacopoeia name, their usual common name or failing this, the chemical name.*Comment: * Please clarify whether excipients should be referred to by the ranking / decreasing priority? Also should all mentioned nomenclature be included?
* Suggest defining the INNM in this sentence as “modified INN”. Also to be revised in Annex, section “Information for the Package Leaflet” –

Proposed change:Proprietary names should not be used for individual excipients. “Excipients should be referred to by their recommended international non-proprietary name (INN or ~~INNM~~ *modified INN*) accompanied by the salt if relevant, or the European Pharmacopoeia name, their usual common name or failing this, the chemical name.” |  |
|  | *Excipients in the labelling*Comment:Recommended to revise the heading as below if the Labelling is referred to the packaging components.Proposed change:“Excipients in the Labelling (outer package, or if no outer package, then on the immediate package):” |  |
|  | *Excipients in the labelling**When a medicinal product contains any of the excipients listed in the Annex, the name of the excipient accompanied by the E number if it exists, or the E number alone must be stated on the labelling.*Comment: The addition of E number should be valid for the leaflet only – as in most case this will take too much space on the labelling. Contradictory to statement above that only E number is requested on labelling – perhaps clarify the relation to the leaflet. |  |
|  | *According to Directive 2001/83/EC, all excipients in parenteral, ocular and topical medicinal products must appear on the labelling*Comment: We would suggest to keep the “ophthalmic” (instead of “ocular”) when referring to medicinal products.Proposed change:According to Directive 2001/83/EC, all excipients in parenteral, ~~ocular~~ *ophthalmic* and topical medicinal products must appear on the labelling. |  |
|  | “*products applied externally to the skin (including transdermal patches), respiratory products delivered to the lung by inhalation and any medicinal product delivered to the ear-, oro-, nasal-, rectal- or vaginal mucosae, i.e. where the delivery may be local or transdermal.*”Comment: We would suggest revising “oro-“ to “oral”, since “oro” is a medical prefix for mouth and the others are not prefixes. To our understanding, the goal was to exclude gastro-intestinally (aka swallowed) disseminated excipients from mentioning on the labeling. We feel this change hardly improves the clarity.Proposed change:*Topical medicinal products can be taken to include those medicinal products applied externally to the skin (including transdermal patches), respiratory products delivered to the lung by inhalation and any medicinal product delivered to the ear-, ~~oro~~ oral-, nasal-, rectal- or vaginal mucosae, i.e. where the delivery may be local or transdermal.* |  |
|  | *“Threshold” subheading*Comment:Please clarify different doses for different patient populations – and how these should be included. E.g. further guidance would be welcomed on how to handle information related to product for which the dose depends on individual patient’s body weight. Should the quantity of excipient be stated by dose per body weight and patient calculate by themselves where they stand? |  |
|  | “*If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it may be better to refer to the amount per tablet, capsule etc.*”Comment:Instructions are provided for solid dosage forms but not for liquids. It could be of value adding guidance for liquids as well similar to the solid dosages. Proposed change: Recommendation shown in red.“If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it may be better to refer to the amount per tablet, capsule etc. If the pharmaceutical form is liquid, it may be better to refer to the amount per millilitre etc.” |  |
|  | Below text has been removed from the revised guideline:“***Information for the Package Leaflet****The text often refers to the term ‘per dose’ meaning dose of the medicinal product. Since doses may be extremely variable, applicants must take into account the maximum single dose of the medicinal product, as defined in the SPC, Section 4.2. For this reason the information sometimes contains the expression ‘up to x mg per dose’, for example.”*Reason for deletion is not clear as this is considered helpful as guidance when authoring package leaflet. |  |
|  | Comment:The current Annex does not distinguish between products containing soya oil and products containing traces of soya protein, e.g. in the form of lecithin (soya), which is a common excipient in film-coated tablets. Subsequent to the adoption of the current excipient guideline, in 2006, the EMA issued a public statement on the Allergenic Potency of Herbal Medicinal Products Containing Soya or Peanut Protein (Doc Ref: [EMEA/HMPC/138139/2005](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089954.pdf)). This document gives specific guidance on soya lecithin and states that the threshold for a contraindication is a specific soy protein content less than 20 μg. Proposed change:We propose that a similar statement is added to the excipient guideline Annex in order to avoid confusion among reviewers and applicants who may otherwise think that any soy content should warrant a contraindication. |  |