Dear Sir or Madam,

Today we would like to inform you about the following topics:

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Best regards

The DiaMed team

1 UPDATED ANNEX TO THE "EXCIPIENTS GUIDELINE"

On October 9th 2017, the *Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'* (EMA/CHMP/302620/2017) has been updated and published with immediate effectiveness. This annex contains a list of all excipients known to have a recognised action or effect and outlines the information which should appear in the package leaflet, for these excipients.

Background: According to Directive 2001/83/EC, all excipients in parenteral, ocular and topical medicinal products must appear on the labelling. For all other medicinal products only the excipients listed in the above mentioned annex to the guideline must appear on the labelling. Irrespective of the route of administration, the advice for all excipients listed in the annex must be included in the package leaflet.

For the first time, the annex is published in all European languages.

With the latest revision of the annex, information on the following 15 excipients has been included or updated:

New:
- Boric acid and borates
- Cyclodextrins
- Fragrance allergens
- Phosphates
- Sodium laurilsulfate

Updated:
- Aspartame and phenylalanine
- Benzalkonium chloride
- Benzoic acid and benzoates
- Benzyl alcohol
- Fructose and sorbitol
- Propylene glycol and esters
- Sodium
- Wheat starch (containing gluten)

In addition, for each of these excipients, a document discussing the scientific background of the update or a Q&A document has been published on the EMA website, as well as a draft Q&A document for ethanol, proposing future changes of the annex which will be implemented in Q2 2018. Proposals for further changes will be published for consultation in Q2 for lactose, polysorbate, L-proline, dextrans and azo-dyes (colouring agents). Subsequently, the following excipients will also be revised: sucrose, polyethylene, glycols (macrogols), maltose, maltodextrin, xylitol and maltitol. A revision of the English version of the annex is scheduled for Q4 with regard to the excipients which have not yet been updated (harmonization with the wording of excipients updated in 2018).

The excipients guideline applies to all national and centrally authorised medicinal products.

For new marketing authorization applications, the updated excipients guideline is to be considered from October 9th 2017 on.

For already authorised medicinal products, marketing authorisation holders should use the first opportunity (i.e. the next type IB or type II variation affecting the product information) to implement the wording in compliance with the revised annex.

For medicinal products with no foreseeable regulatory submissions, marketing authorisation holders should submit a type IB variation within 3 years after publication of the revised annex of the excipients guideline (i.e. until October 9th 2020 at the latest).

For purely nationally authorised products in Germany, for which the implementation of the updated annex of the excipients guideline would lead to significant deviations from the requirements of the current "Besonderheitenliste", it may be advisable to postpone the text changes, because BfArM has indicated in the annual meeting with the BPI (German Pharmaceutical Industry Association), that a national guidance document for the implementation will be published, particularly for those specifications of the updated annex which are "not always 100 % precise". The date of the finalisation of these national implementation rules has however not been set, yet.

2 OBLIGATION TO STATE THE STRENGTH OF HERBAL MEDICINAL PRODUCTS

Based on a decision of the Administrative Court of Cologne dated 26.04.2016 (7 K 2617/14), BfArM changed his administrative practice: For all new marketing authorisation procedures for herbal medicinal products (authorisation, registration), from now on the strength must be included in the name of the medicinal product and consequently in the product information (SmPC, PIL, labelling).

For already authorised or registered herbal medicinal products, the addition of the strength has to be submitted in the context of the renewal of the authorisation/registration or in variations for name changes. For medicinal products with an unlimited authorisation according to § 31, 1a of the German Medicinal Products Act or for which no variations to change the name are planned, pharmaceutical companies are requested to take responsibility to include the strength as soon as possible, but at least within 5 years, as part of any change notification or variation affecting the product information. In justified individual cases or in the interest of uniformity and transparency, BfArM reserves the right to mandate the inclusion of the strength.

3 Q&A ON DRUG SUBSTANCE STARTING MATERIALS (ICH Q11)

In September 2017, the EMA has published a Q&A document (EMA/CHMP/ICH/809509/2016) pertaining to the ICH Q11 guideline *Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)* in order to clarify issues relating to the selection and justification of starting materials as well as to the information to be provided in the quality dossier and/or master files, with focus on chemical entity drug substances. It will become effective on February 28th 2018.