Dear Sir or Madam,

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

1 UPDATED ANNEX TO THE “EXCIPIENTS GUIDELINE”: 2
CORRECTIONS OF APPENDIX AND DISCUSSION ON FURTHER EXCIPIENTS 2
2 AMG-NOVELLE (AMENDMENT TO GERMAN MEDICINAL PRODUCTS ACT): DRAFT LAW FOR MORE SAFETY IN SUPPLY OF MEDICINAL PRODUCTS....3
3 IMPLEMENTATION AND TRACKING OF GRADUATED PLAN DECISIONS, SIGNAL MANAGEMENT AND PSUSA OUTCOMES....4

Please pay attention to the following deadlines:

We are at your disposal, should you require assistance or have further questions.

Best regards

The DiaMed Team

1 UPDATED ANNEX TO THE "EXCIPIENTS GUIDELINE": CORRECTIONS OF APPENDIX AND DISCUSSION ON FURTHER EXCIPIENTS

In our newsletter dated 31st January 2018 we informed you about the updated annex of the "*Guideline on excipients in the labelling and package leaflet of medicinal products for human use*" dated 09th October 2017. A revised version of the guideline itself was published in March 2018.
By the end of 2018, EMA informed about minor corrections regarding the revised sections of the annex. In addition, further excipients and the related information for inclusion in the package leaflet and labelling were presented for discussion.
The following sections of the annex of the excipients guideline, revised in 2017, were corrected on 19th November 2018 as follows:

- **Phenylalanine:** The route of administration, for which the information has to be inserted in the package leaflet, has been changed from "oral" to "all".
- **Sodium laurilsulfate:** The E number has been deleted.
- **Wheat starch (containing gluten):** The wording of the requested information in the package leaflet has been changed.

The listed changes are outlined at the end of the annex in the newly inserted section "Corrigendum 1 (19/11/2018)". The updated version is available on the EMA-Website in all European languages.

Marketing authorization holders should implement the new wordings within a three-year period preferably in the scope of a type IB variation. The EMA does not comment on a prolonged grace period for implementation regarding the corrected excipients. In addition, it remains unclear how to proceed, if marketing authorization holders have already implemented the information on wheat starch in line with the version before correction.

Furthermore, the EMA has presented further draft versions regarding information for inclusion in the package leaflet:

- **Proline**
- **Polysorbates (E 432 – E 436)**
- **Lactose**
- **Dextrans (parenteral and inhalation)**

Comments on these draft versions should be submitted directly to EMA until 31st May 2019, or can be reported to German pharmaceutical associations BPI or BAH until 30th April 2019.
The excipients guideline applies to all national and centrally authorised medicinal products.

An overview on the current state of progress as well as links to the final and draft documents on each individual excipient can be found in the EMA section Excipients labelling.

2 AMG-NOVELLE (AMENDMENT TO GERMAN MEDICINAL PRODUCTS ACT): DRAFT LAW FOR MORE SAFETY IN SUPPLY OF MEDICINAL PRODUCTS

The German Federal Ministry of Health has submitted a draft law for more safety in supply of medicinal products (GSAV: "Gesetz für mehr Sicherheit in der Arzneimittelversorgung") in November 2018 (updated in January 2019). The law intends to implement safety measures due to experiences from execution processes and other events from the recent past (Valsartan, Lunapharm, incorrect dosing of cancer drugs by a pharmacist from Bottrop). The law includes changes in the Medicinal Products act ("Arzneimittelgesetz", AMG), which are also relevant for regulatory affairs.

The law is an omnibus act ("Artikelgesetz") which comprises changes of further laws and regulations besides the AMG.
The changes in the German medicines act related to approval of medicinal products are summarized below:

Labelling (§ 10) – *"verwendbar bis" can be shortened as "verw. bis"*
The requirements resulting from the Falsified Medicines Directive from February 2019 onwards addressing the labelling with safety features on outer packages demand greater space requirements for the labelling elements.
The possibility to alternatively use a shortening of the note "verwendbar bis" (Expiry date) increases flexibility of manufacturers, especially for medicinal products marketed in small packages.

Information for the public (§ 34) – ***Name and address of API manufacturer***
The higher federal authority is obligated to provide name and address of the manufacturer(s) of the API (acc. to § 22 (2) No. 8) through its web portal (acc. to § 67a Section 2 AMG).

Authorization for standard marketing authorization („Standardzulassung") (§ 36) - *Removal of expert consultation*
The instrument of standard marketing authorizations has been on trial for years and is now intended to be gradually reduced. Existing monographs have to be regularly adapted according to the current state of science and technology, but new medicinal products shall not be exempted from the obligation of individual authorization. The process will be simplified, since expert consultation and the previously required agreement of federal council will be deleted from the law.

Medicinal products for treating haemophilia (§ 47) – *distribution channel*
Regarding medicinal products for treating haemophilia, purchase and administration will be separated again in the future. In order to achieve greater control of the distribution channel, the distribution of all medicinal products for specific therapy of clotting disorders under haemophilia will be restricted to pharmacies.

Prohibitions and authorizations to protect health (§ 6) – *Prohibitions, listing of substances*
The current legal basis is supplemented by a prohibition to manufacture, market, or apply medicinal products, if the manufacturing process violates the requirements of a corresponding implementing decree. Furthermore, a new annex contains a concrete list of substances, preparations made from substances, and objects which are regulated (e. g. aflatoxins, ethylene oxide, colourants, fresh cells, as well as substances of animal origin carrying the risk of transmitting transmissible spongiform encephalopathy).

Higher federal authorities (§ 69) – *Extended competencies*
Changes will be made with respect to the incidents of falsified or contaminated medicines, comprising among others the extension of recall competence of the higher federal authorities and a strengthening of the regulatory coordination role in case of threatening supply shortage. The coordination role of the federal authorities is to be especially focused on the actions after recall of medicinal products associated with quality defects of active substances.

3 IMPLEMENTATION AND TRACKING OF GRADUATED PLAN DECISIONS, SIGNAL MANAGEMENT AND PSUSA OUTCOMES

During the last routine session of pharmacovigilance officers in November 2018 at the Federal Institute for Drugs and Medical Devices (BfArM), new regulations on the implementation and tracking of graduated plan decisions, signal management and PSUSA outcomes were subjects of discussion. According to current law (§ 11 of German Medicines Act (AMG)) marketing authorisation holders *are required to keep the package leaflet scientifically up-to-date, which includes the conclusions of assessments and recommendations published on the European internet website set up pursuant to Article 26 of Regulation (EC) No. 726/2004.*
This also includes PRAC recommendations resulting from signal management, as well as outcomes from PSUSA procedures. An implementation of risk minimizing actions is therefore fixed by law and has to be followed by all marketing authorization holders.

PRAC recommendations
The recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC), which are derived from signals referring to risks of human medicines, are published on the EMA website under *PRAC recommendations on safety signals.* An EPITT number is provided for each signal. EPITT stands for "Pharmacovigilance Issues Tracking Tool" and allows EMA to perform a web-based detection, assessment, and processing of signals.
Usually, changes in the summary of product characteristics and package leaflet based on PRAC recommendations have to be notified as category C.I.z, variation IA_{IN} according to the European Commission guidance C(2013)2804 from 16th May 2013. If no other timeline is mentioned on the above mentioned EMA website or in the context of German translations, in urgent cases the variation has to be submitted **within one month**, in all other cases within two months.

In order to simplify the information and implementation of PRAC recommendations resulting from signals for the MAH, the BfArM publishes a list of signals associated with intended text corrections in a new section. The changes in the product information texts have to be adapted in the German wording without deviations.
https://www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/Textanpassung/_node.html
This list contains the names of the active substances and the signal (contained in the heading referring to the corresponding PRAC recommendation), a link to the corresponding PRAC recommendation as well as an SKNR number linked to the EPITT number of the EMA, which has to be assigned on submission of the corresponding variation and which serves as a base for checking if the variation has been submitted.

PSUSA Outcomes
If the scientific evaluation in the scope of a PSUSA procedure requires the change of a marketing authorization, this represents the current scientific knowledge which has to be implemented by a suitable regulatory procedure (e. g. variation) by all MAHs of medicinal products containing the active ingredients affected by the PSUSA procedure.
https://www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/PSURs/psusa/_node.html
MAHs which have not participated in a PSUSA procedure should inform themselves about upcoming variations via the PRAC minutes early on, a specific need for action only exists upon publishing by CMDh or EC.

Traceability/Review
In the future, the BfArM will regularly review whether required actions are implemented in the scope of a safety variation. Indication of the SKNR number (signal procedures: SKNR 6336; PSUSA procedures: SKNR 6183) linked with the corresponding EPITT or PSUSA number is mandatory. The review has now been established since January 2019 by sending reminders to the MAHs. A submission deadline of two weeks after receipt of the reminder will be granted. If changes are not implemented in time, the BfArM will consider further actions like administrative offences or MA suspension/withdrawal.