Dear Sir or Madam,

Today we would like to provide further information about the following topics:

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

Best regards

The DiaMed Team

1 RISK EVALUATION ON THE PRESENCE OF POTENTIAL NITROSAMINE IMPURITIES

As a result of the contamination of nitrosamines in sartans, pioglitazone and ranitidine in the past year, the EMA has requested all marketing authorization holders (MAHs) of medicinal products containing chemically synthesised active pharmaceutical ingredients (APIs) to assess the risk of the occurrence of nitrosamine contamination and, if necessary, to take appropriate risk mitigation measures.

The corresponding letter from the EMA dated September 19th 2019

- describes the background of the contamination of APIs with nitrosamines,
- clarifies the responsibilities of MAHs,
- identifies potential sources of nitrosamine contaminants,
- calls for a three-step assessment procedure:

Step 1: Risk evaluation

For medicinal products containing chemically synthesized APIs, MAHs are required to perform a risk assessment no later than 6 months after publication of the EMA letter (i.e. no later than 26 March 2020). The information necessary for risk evaluation should be made available to the MAHs by the API manufacturers. The competent authority should be informed when the risk evaluation has been concluded.

With regard to the potential risk, MAH should prioritise their products within the 6-month period. For medicinal products presenting a high risk of potential nitrosamine contamination, the evaluation should be carried out immediately.

The risk evaluation should be performed in accordance with the principles of the following ICH Directives

- ICH Q9 *Quality Risk Management*
- ICH M7 *Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*

Stage 2: Confirmatory studies

Where a risk of presence of nitrosamines has been identified, it shall be verified using appropriately validated and sensitive methods.

Again, high risk products should be clearly prioritised. The results of the investigations must be completed no later than 3 years after publication of the EMA letter (i.e. no later than 26 September 2022).

In the case of confirmed presence of nitrosamine impurities (irrespective of the quantity detected), the competent authority should be informed immediately.

Stage 3: Modification of the approval documents

In the event of required changes, e.g. to the manufacturing process or product specifications, corresponding variations to introduce these changes should be submitted within 3 years of publication of the EMA letter (i.e. by September 26th 2022 at the latest).

If any finding indicates an immediate risk to public health, authorities must be informed immediately.

Further information can be found in a Question & Answers document issued by the EMA.

2 SUNSET CLAUS IN GREECE

In Greece, the EOF (National Organization for Medicines) now also monitors the marketing status of marketing authorisations (MAs).

- Any MA that has not been placed on the market within three years of the authorisation expires and is automatically revoked once the EOF has established that the MA has been withdrawn.
- Any MA for a medicinal product placed on the Greek market which has been suspended for three consecutive years will expire and be automatically withdrawn upon EOF determination.

The EOF will send the MAHs a list of their expiring MAs based on sunset clause provisions, in particular for those MAs that expired on December 31st 2018.

MAHs must confirm the accuracy of the marketing status information in the list and notify the EOF in writing by October 31st 2019 whether or not they wish to exempt these products from sunset clause implementation. If an exemption is requested, the request must be adequately justified.

The request for exemption must be submitted to the protocol department with the subject "SUNSETCLAUSE" electronically to the e-mail address sunset2019@eof.gr.

If you have not received such a list, please check whether you have products for which there was no actual placement on the Greek market until December 31st 2018.

3 AMENDMENT OF THE GERMAN MEDICINAL PRODUCTS ACT

In February of this year, we already reported on the draft law for more safety in the supply of medicinal products ("Gesetz für mehr Sicherheit in der Arzneimittelversorgung") and the associated changes relevant to marketing authorisations.

Article 1 of the AMVSÄndG, which contains numerous amendments to the German Medicinal Products Act (AMG), entered into force on August 16th 2019. For an overview of the amended individual standards, please refer to the synopsis of all amendments of the AMG published in buzer.de, can be found at: https://www.buzer.de/gesetz/7031/v225653-2019-08-16.htm.

4 MUTUAL RECOGNITION AGREEMENT (MRA) ON GMP INSPECTIONS OF MEDICINES MANUFACTURERS BETWEEN THE EUROPEAN UNION AND THE USA

The EU and the USA signed an mutual recognition agreement (MRA) on GMP inspections in February 2017, which enters into force on November 1st 2017. With this agreement the regulatory authorities agreed to mutually rely on inspections of manufacturing sites for human medicines so that - unless under exceptional circumstances - there is no need for an EU authority to inspect a site located in the USA. This is also applicable vice versa, provided that the respective EU authority was already assessed by the FDA.

This process has now been completed, i.e. all European authorities have been approved by the FDA. A Q & A document on the consequences, e.g. regarding batch testing (Q10), can be found at https://www.ema.europa.eu/en/documents/other/questions-answers-impact-mutual-recognition-agreement-between-european-union-united-states-11-july