Annex II

Amendments to the conditions to the marketing authorisation(s)

Conditions to the MA	Due date
The MAH must ensure that the manufacturing processes of the active substances used for their finished products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products (Article 5(3) procedure).	17 April 2021
The MAH must ensure that the manufacturing processes of the finished product is reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible in line with the recommendations adopted by the Committee for Medicinal Products for Human Use on 25 June 2020 in the procedure under Article 5(3) of Regulation (EC) No 726/2004 on Nitrosamines impurities in human medicinal products.	26 September 2022
For all N-nitrosamines, the MAH must ensure a control strategy is in place for active substance batches used for their finished products.	17 April 2019 (last date of the Commission decisions related to the Article 31 referral adopted in 2019[1])
For N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA) the MAH must introduce the following specifications: Limits for NDMA (96 ng/day) and NDEA (26.5 ng/day) should be implemented for the finished product. The limit should be calculated by dividing the respective limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC. The limit will usually need to be included in the finished product specification. Omission from the specification is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 10% of the limit defined above and the root cause is identified and well-understood. Skip testing is only justified if it can be shown that the levels of the respective N-nitrosamines are consistently ≤ 30% of the limits defined above and the root cause is identified and well-understood. In accordance with the recommendations adopted on N-nitrosamines impurities in human medicinal products (Article 5(3) procedure), where the co-presence of the above N-nitrosamines has been identified in the same finished product, it must be ensured that the cumulative risk of these N-nitrosamines does not exceed a lifetime cancer risk (lifelong exposure) of 1:100,000. An alternative approach where the sum of these two N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified (NDEA) may also	30 June 2021

[1] Commission Implementing Decision C(2019)3157 (final) of 17.4.2019 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisation granted by Decision C(2016)1906(final) for "Amlodipine/Valsartan Mylan - amlodipine/valsartan", medicinal product for human use

be used. The approach chosen for a particular case needs to be duly justified by the MAH. The MAH shall ensure that the control strategy for all N-nitrosamines is updated accordingly.	