**EFPIA response to Pharmeuropa Issue 32.2 proposal for chapter 2.4.36 ‘N-Nitrosamines in Active Substances’**

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# General Comments

EFPIA understands this new chapter is intended to be complementary to regulatory responses to the discovery of N-nitrosamine impurities in certain medicinal products, initially related to certain sartan medicines, and supports efforts to strengthen the protection of public health on this issue.

EFPIA believes the text should clearly limit the use of these methods for the five sartan active substances listed in the text. There should be no reference to their use for other materials or products.

Sample preparation, chromatography and spectrometric conditions would potentially need considerable adaptation for other active substances, other substances for pharmaceutical use, and medicinal products. Without suitable development and validation, there is a risk of erroneous results arising from matrix effects due to other materials in products that may contain nitrosamines as potential contaminants, and other active substances could potentially give rise to the formation of different nitrosamine impurities. These factors would obviously impact the suitability of these methods for other applications.

The limitation of the methods to sartans and the listed nitrosamines should be reflected in the title. As it stands the title suggests the chapter covers, and that the methods are suitable, for any N-nitrosamine in any active substance.

EFPIA would welcome the opportunity for further discussion about the technical challenges and approaches used for the testing and control of nitrosamine impurities.

# Specific Comments on the Proposed Text

EFPIA welcomes the opportunity to make the following comments on the proposed new chapter 2.4.36:

* EFPIA notes that the analytical procedures are for application to the five active substances shown in Table 2.4.36-1 and that the text is limited to use for the Active Pharmaceutical Ingredients (API) listed in the text. If the procedure is to be applied outside the scope shown in the Table then the procedure should be further validated. However, the European Pharmacopoeia is used as a reference in markets outside of Europe and in some cases regulatory agencies may (mistakenly) mandate the use of the published methods for all APIs. Given the analytical challenges associated with the determination of N-Nitrosamine impurities to avoid false positive or negative results, to avoid this misinterpretation we suggest deletion of the following text from the chapter – ‘*When a procedure is applied to substances outside of the scope covered by the initial validation (see Table 2.4.36.-1) or to medicinal products or is used quantitatively, then it must be validated*’. Experienced analysts and users of the Pharmacopoeia will understand that if methods A, B and C are to be applied to situations outside of the scope shown in Table 2.4.36-1 then the procedure should be validated.

Further to the above, EFPIA believes the title of this Chapter is misleading with respect to “N-Nitrosamines”. There are hundreds of potential N-nitrosamines but the text is only addressing the seven that have been observed in individual sartan drugs. The title as given creates the expectation that the methods provided allow for testing any nitrosamine in any active substance.

We suggest changing the title to

“N-Nitrosamines in angiotensin-II-receptor antagonists (Sartans) containing a tetrazole group”

per EU publication “Sartans-article-31-referral-chmp-assessment-report” of 14 Feb 2019. The original title implies applicability to all active substances, and the method scope is only for 5 Sartans.

* EFPIA recommends this chapter is applied by cross reference in specific sartan active substance monographs

# Detailed comments

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| 1 | Method Parameters | Specificity to instrument | We recommend further consideration is given to the level of specificity needed in the details of the procedure for it to be successfully used by the user of the pharmacopoeia.  There may be a need for adjustment of parameters based on type of instrument and ion source design.  Collision energy values will need to be optimised for different instrument manufacturers, as it is not possible to directly use the same values to produce the same level of fragmentation across different instrument platforms. Collision gases and pressures will vary. Fragmentor voltage is not a parameter found on all instruments.  Details of the validation and specific instrument used in the procedure could be helpful to the user of the pharmacopoeia. |
| 2 | Method A and C | Method specificity | For the GC-MS and GC-MS/MS method, the station phase and film thickness in the proposed methods may not be the optimum and/or the only option. Consideration should be given to allowing any stationary phase with certain film thickness that can provide acceptable peak shape and selectivity for the analysis of the specified Nitrosamines. |
| 3 | Standards procedure A utilises deuterated N-Nitrosodiethylamine NDEA-d10) as an internal standard, whereas method B and C use N-Nitrosoethylmethylamine NEMA as an internal standard | Measurement uncertainty | Deuterated internal standards (NDEA-d10) provided inherently greater accuracy and precision when compared to use of a structurally similar internal standard (NEMA). It would be helpful to understand if differences in measurement uncertainty were observed when using the two different internal standards |
| 4 | Terminology | Description of mass spectrometer - ion source and collision cell (MRM) parameters | Page 2 lines 15-18: Detector is not the correct terminology - these are mass spectrometer ion source and collision cell (MRM) parameters. We suggest the following text for consideration:  "if the mass spectrometer has different settings (different manufacturer, for example), optimise the ion source and MRM parameters...." |
| 5 | Signal to noise ratio | S:N calculation | Is greater clarity required for the S:N calculation because of the need to determine trace levels of nitrosamines? Many software packages can automatically calculate S:N but the algorithm used may not be apparent |
| 6 | Scope of Validation | Potential interference | If DMF is used in the API synthesis then LC-MS/MS without high MS resolution may be a sub-optimal approach for testing NDMA due to the potential DMF interference. Was interference by DMF evaluated in the development/validation of these methods?  Method A risks potential false positives due to DMF for NDMA analysis. Resolution of DMF and NDMA in Methods B and C would also be a concern. |