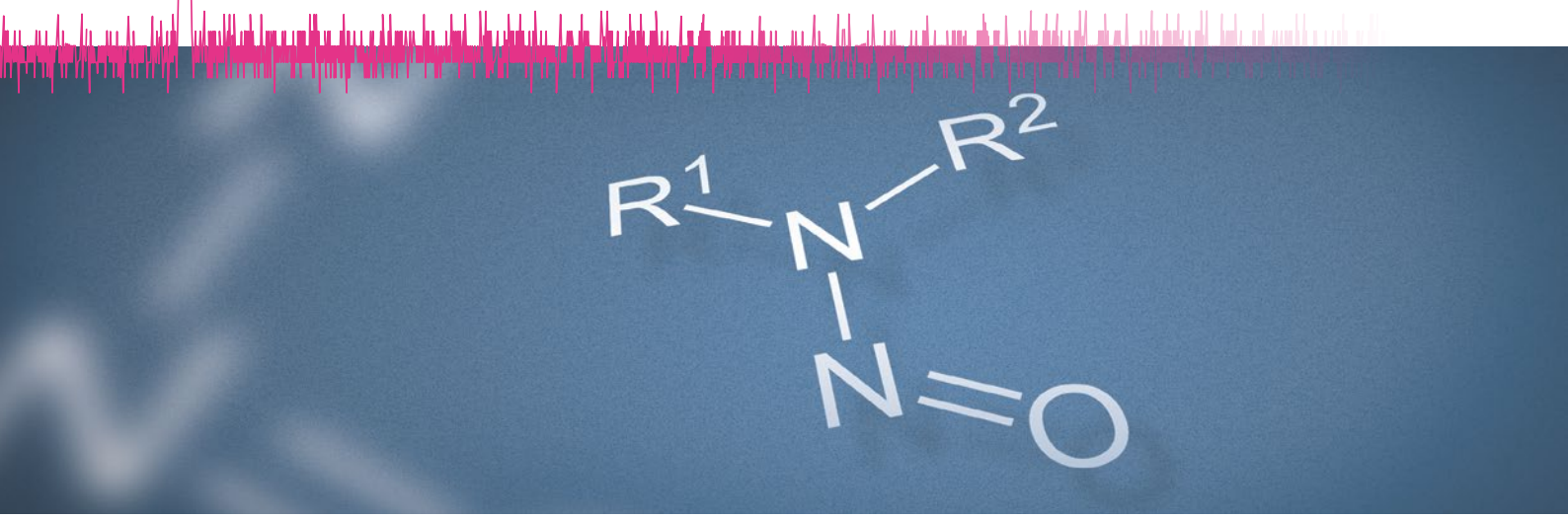
INTERLABOR
BELP AG

FACTSHEET



Nitrosamine contamination of active pharmaceutical ingredients and finished products

Introduction

Since the discovery of appropriately contaminated batches of the API valsartan of a Chines manufacturer by the authorities in the summer of 2018[1], nitrosamine contaminations have been discovered in products of other manufacturers as well as in other active ingredient classes.
The consequences were global product recalls and a high level of uncertainty among producers and consumers.
In response to the high levels of contamination that had happened, in future the EMA will require every marketing authorization holders to ensure that every medical product for human use is nitrosamines free[2]. It is also necessary to carry out a risk analysis for each product[2]. In recent months, the FDA, Swissmedic and other authorities have published numerous methods for analyzing nitrosamines in APIs and finished products. Each of these methods has advantages and disadvantages. However, there is no generally standardized procedure.
Here at Interlabor, we would like to help you in risk assessment and present you with a concept for determination of nitrosamines.

Analysis of nitrosamines

INTERLABOR Belp AG favours a GC-MS/MS procedure from Swissmedic.
An extensive basic verification has already been successfully completed. Therefore, the analysis of future samples can be performed directly within the accreditation after a product-specific verification with reduced scope.
Alternatively, an HPLC-MS/MS method developed by INTERLABOR Belp AG is available. Depending on the API, required limit of detection and matrix, the optimal analytical method can be applied. Currently the following nitrosamines can be determined:

- **NDMA (CAS 62-75-9)**
- **NDEA (CAS 55-18-5)**
- **NDPA (CAS 621-64-7)**
- **NDBA (CAS 924-16-3)**
- **NDIPA (CAS 601-77-4)**
- **NEIPA (CAS 16339-04-1)**

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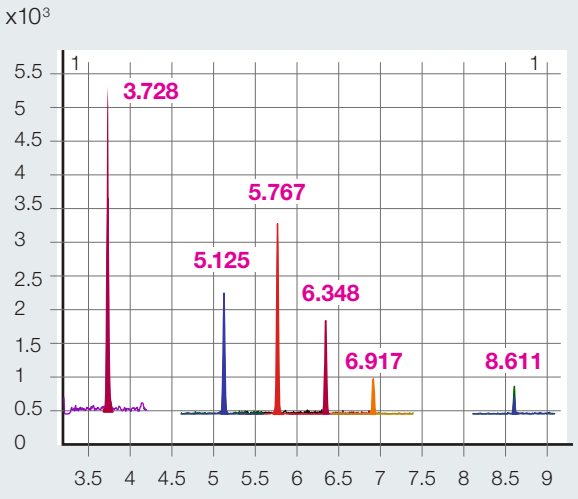
In addition, the testing of nitrosamines required by Ph. Eur. since January 2020 can be performed in the following active ingredients:

- **Candesartancilexetil (2573)**
- **Irbesartan (2465)**
- **Losartan-Kalium (2232)**
- **Olmesartanmedoxomil (2600)**
- **Valsartan (2423)**

Example chromatogramm nitrosamine analytes



Counts vs. Acquisition Time (min)

Retention time (minutes)

3.728	NDMA	N-Nitrosodimethylamine	(CAS 62-75-9)
5.125	NDEA	N-Nitrosodiethylamine	(CAS 55-18-5)
5.767	EIPNA	Ethylisopropylnitrosamine	(CAS 16339-04-1)
6.348	DIPNA	N-Nitroso-di-iso-propylamine	CAS 601-77-4)
6.917	DPNA	N-Nitroso-di-n-propylamine	(CAS 621-64-7)
8.611	DBNA	N-Nitroso-di-n-butylamine	(CAS 924-16-3)

Key facts analysis of nitrosamines at INTERLABOR Belp AG

Option A:
analysis of nitrosamines under the quality state of the art

- Analysis of the first sample including recovery (*n* = 1; 100 % level): 1750 CHF
- Analysis of each additional sample of the same series: 675 CHF
- Processing time: 15 working days
- Indication of API concentration, maximum daily dose and tablet weight

Option B:
analysis of nitrosamines under the quality state of the art

- Analysis of the first sample including selectivity, recovery (*n* = 3; 50 %, 100 %, 150 % level) and linearity (*n* = 5; 50 % - 200 % level): 5640 CHF
- Analysis of each additional sample of the same series: 675 CHF
- Processing time: 15 working days
- Indication of API concentration, maximum daily dose and tablet weight

References

1. *https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities*
2. *https://www.ema.europa.eu/en/news/ema-advises-companies-steps-take-avoid-nitrosamines-human-medicines*

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