Impurity Analysis in API and Drug Product Using Orbitrap – Quantitation of N-Nitrosodimethylamine (NDMA) –

N-Nitrosodimethylamine (NDMA) is known as a carcinogenic substance. The NDMA can be generated in the manufacturing process of API (active pharmaceutical ingredients) or drug product under the existence of nitrous acid, if the structure has a dimethylaminomethyl group. The authorities specify an allowable NDMA intake amount, and it is very important to evaluate the NDMA content in API /drug product.

Limit of Impurity in API

The FDA and EMA have notified that NDMA, a carcinogenic substance, was detected from a ranitidine hydrochloride (API) /drug substance, which is classified as a histamine H_2 receptor antagonist. Therefore, the authorities required manufacturers to evaluate that NDMA contents in their drug substances are below the control level. The same action is required also for Nizatidine (API) having a chemical structure similar to Ranitidine.

Category	Component	Maximum daily intake (mg)	Limit of NDMA in drug substance (ppm)
Histamine H_2-receptor antagonist	Ranitidine	300	0.32
	Nizatidine	300	0.32

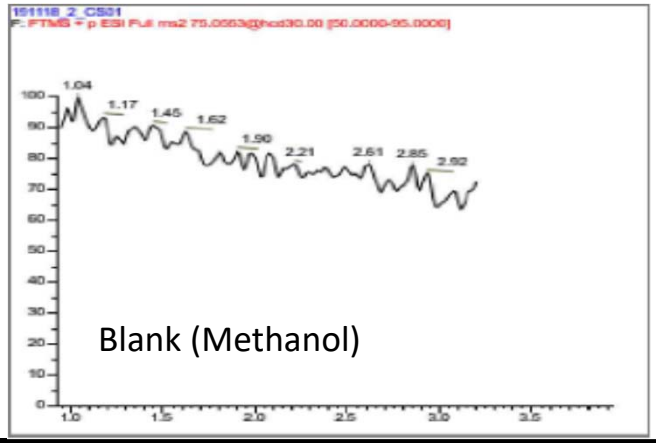
The limit (0.32 ppm) was calculated based on the allowable intake (0.0959 µg/day).

NDMA Measurement (Blank Sample and Lower Limit of Quantification)

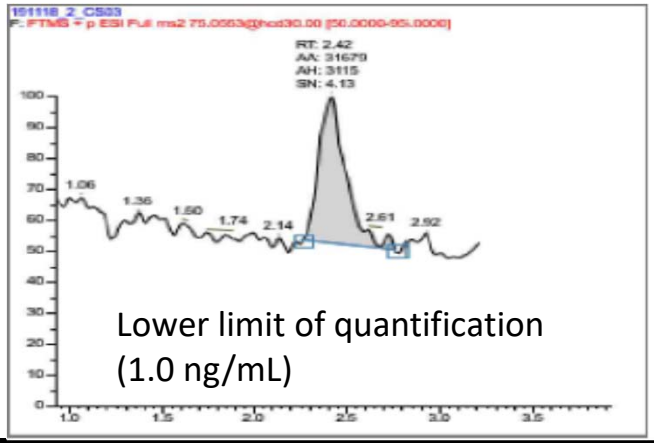
Improved the NDMA analytical method indicated by the FDA and developed an analytical method with better quantitative performance.

Instrument：Orbitrap Fusion Lumos (Thermo fisher scientific)
*https://www.fda.gov/media/130801/download

- Quantification range　1.00 - 100 ng/mL (5 points)
- Linearity　Correlation coefficient: more than 0.99
- Reproducibility　%CV less than 5% (2 ng/mL, n=6)



Blank (Methanol)



Lower limit of quantification (1.0 ng/mL)