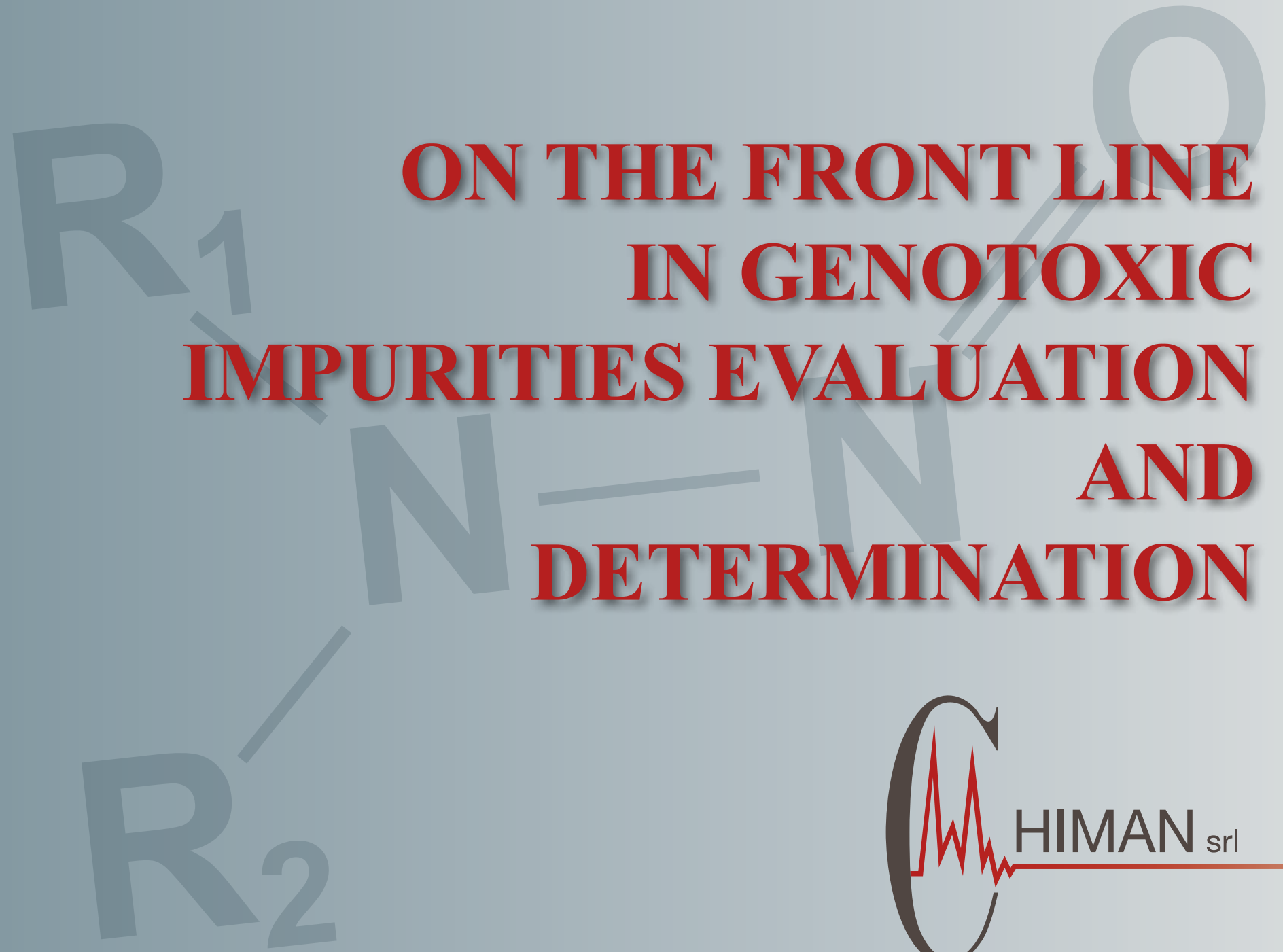
ON THE FRONT LINE IN GENOTOXIC IMPURITIES EVALUATION AND DETERMINATION



CHIMAN srl

NITROSAMINES

N-Nitrosamines Contamination

N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), both classified as probable human carcinogens, were not identified as impurities of Sartan APIs and now the same problem was found in Ranitidine HCl drug product.

Sodium azide, Zin Chloride in presence of Dimethyl formamide giving quenching with sodium nitrite transformed it in nitrous acid. Nitrous acid fast reacting with secondary amines gives N – Nitrosamines, classified as human carcinogens.

Sisthema & Chiman Services

Sisthema and **Chiman** have joined their competences to guarantee within specification levels of N-Nitrosamine Impurities API's and Drug Products, **Chiman** uses LC-MS/MS methods in accordance with EDQM and FDA methodology.

Sisthema risk analyses approach is based on a long experience in application of risk management tools based on ICH Q9 guideline to several aspects of the pharmaceutical manufacturing.

ICH Q3D approach will be applied and customized on clients needs.

Chiman Laboratory following evidence of the risk assessment is able to develop methodologies and analytical testing plans in order to sustains risk-based considerations. **Chiman** quality assurance approach is based on state-of-the-art analytical equipment, completely in accordance with CFR21 requirements.

Acceptance Limits

Regulatory expectation is a non-quantifiable level of N-nitrosamine. Some drugs have been under investigation by the Regulatory Agencies and temporary acceptation limits were put in place, depending on the maximum daily intake of the drug product. N-Nitrosamines Acceptable Intakes (AIs) on which temporary limits should be based, are available for NDMA, NDEA, NMBA, DIPNA and EIPNA impurities.

Chiman has invested in a UPLC – Orbitrap Q Exactive Classic, to be able to detect those impurities at the lowest regulatory level set.

Other API's and Drug Products are under investigation by the European Medicine Agency and FDA, in order to increase safety and quality of the Medicinal Products potentially contaminated by those impurities.

Methods for the determination of such kind of impurities in Sartans, Ranitidine, antibiotics like Cefazolines, Omeprazole and others branded drugs according to the clients need, will be developed in the next months.

Risk Assessment

Sisthema can provide an experienced support to Clients, in order to obtain a Robust Risk Assessment, based on ICH Q3D guideline on Elemental Impurities.
www.sisthema.biz

Analytical Methodologies

Following FDA methodologies like FY19-107-DPA-S_LC-MS Method for Detection of Six Nitroso Impurities in angiotensin II receptor blocker Drugs_051619, Chiman can provide UHPLC-ESI-APCI-MS/MS analysis of N-Nitrosamines in API's and Drug Products by using official methods or customized methods on Client's needs.

All the methods will be validated according to ICH Guidelines, before their use.

All the regulatory Agencies investigation up-grades will be integrated in **Chiman** methodologies.

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