By: Philip J. Koerner, Ph.D. - Global Industry Manager - Pharmaceutical

The Korea Food and Drug Administration (KFDA), in cooperation with SCIEX Korea, has recently published an official LC-MS/MS method using Kinetex® F5 (2.6 µm 100 x 3.0 mm) column for the determination of N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in drug products, such as valsartan. NDMA and NDEA impurities have been reported to be found in several drug products and this method will allow for testing of both API and drug products for the presence of these impurities.* NDMA is highly toxic and is a known carcinogen in lab animals, and along with NDEA has been classified as a probable human carcinogen.

Valsartan and other related ‘sartan’ medicines are used to treat patients with hypertension (high blood pressure), and those with heart failure or who have had a recent heart attack. Sartans work by blocking the action of angiotensin II, a hormone that constricts blood vessels and causes blood pressure to rise.

Earlier this summer the U.S. Food and Drug Administration (FDA) issued a recall for several drug products containing Valsartan, due to the potential presence of the impurities NDMA and NDEA. More recently, additional products have been voluntary recalled by the manufacturers for drug products containing Irbesartan (labeled as Westminster Pharmaceuticals Inc. and GSMS Inc.) and Lorsartan (Sandoz drug product containing losartan potassium and hydrochlorothiazide). NDMA and NDEA are not expected impurities and are believed to have been introduced into the drug products because of the specific sequence of manufacturing steps and chemical reactions used to make the drug substance. As a result, two Chinese API manufacturers have been prohibited from exporting Valsartan into the United States and Europe.
The European Medicines Agency (EMA) has recently expanded its own review of NDMA and NDEA impurities in Valsartan to more broadly target other sartans (Candesartan, Irbesartan, Losartan and Olmesartan). This action followed the detection of trace levels of NDEA in another active drug substance, Losartan, manufactured in India. While the source of these impurities has not yet been established, valsartan and these other sartans have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of impurities such as NDEA. The European Directorate for the Quality of Medicines (EDQM) has also published methods to detect NDMA and NDEA.

Both FDA and EMA will continue providing regular updates as additional information becomes available.

* FDA has posted two methods (GC-MS headspace and GC-MS/MS liquid injection) for simultaneous determination of NDMA and NDEA from API and drug products

Related Technical Notes:
LC-MS/MS Method for Determination of NDMA and NDEA in Valsartan

NDMA and NDEA detection with SCIEX 5500 system

**MS ion source parameter**
- Ion source: APCI
- Polarity: Positive
- Nebulizer current: 3
- Source temperature: 500

**HPLC condition**
- Columns: Phenomenex Kinetex F5 (3.0 x 100mm, 2.6um)
- Mobile Phase A: Water
- Mobile Phase B: Acetonitrile
- Flow rate: 0.4 mL/min
- Column temperature: 40
- Injection volume: 20μL

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Divert valve: Initial (Waste) – 1.5 min (MS) – 5.3 min (Waste)

Figure 1: NDMA

Figure 2: NDMA-d6

Figure 3: NDEA
LC-MS/MS Method for Determination of NDMA and NDEA in Valsartan
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