RISK ASSESSMENT STUDY OF *N*-NITROSAMINES IMPURITY IN CEFPODOXIME PROXETIL

As great concern shown by the European Medicine Agency (EMA) and other regulatory agencies across the globe, regarding the N-nitrosamines impurity (mainly NDMA & NDEA), which are classified as probable human carcinogen. Therefore, this becomes mandatory for all the API's manufacturers and stakeholders to show its absence study or control strategy in the finished product, through Quality Risk Management study.

Nitrosamine impurity, which is a Genotoxic impurity can form during API synthesis under certain processing conditions, discussed below;

(Reference: European Medicines Agency, EMA/189634/2019&EMA/428592/2019)

1. The use of Sodium Nitrite ($NaNO_2$), or other nitrites in the presence of secondary or tertiary amines.
2. Amide solvents such as *N, N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), or *N, N*-dimethylacetamide (DMA), can degrade to secondary amines, which are known source of nitrosamines.
3. Tertiary amines *viz.* triethylamine, diisopropylethylamine etc., are common bases which have already been observed to allow nitrosamine formation.

Quality risk Management Process for Cefpodoxime Proxetil:

As outlined in ***ICH Q9 guidelines***, quality risk management can be performed through following steps discussed below:

Step-1: Initiating a quality risk management process

..... drugs limited has evaluated the synthetic route for the preparation of Cefpodoxime Proxetil and other possible pathway responsible for generation of genotoxic impurity such as *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA).

Step-2: Risk assessment

..... has identified use of sodium nitrite in the preparation of side chain MAEM, which is procuring from vendor.

- **Risk identification:**

1. Use of sodium nitrite at Stage-1 of the preparation of MAEM (at vendor site)

2. Use of triethylamine at Stage-6 of the preparation of MAEM (at vendor site).
3. Use of triethylamine at Stage-2 of the preparation of Cefpodoxime Proxetil (at site).
4. Use *N*,*N*-dimethylacetamide (DMAc) at Stage-3 and Stage-4 of the preparation of Cefpodoxime Proxetil (at site).
5. Use of 1,1,3,3-Tetramethylguanidine (TMG) at Stage-4 of the preparation of Cefpodoxime Proxetil (at site).

- **Risk analysis: There is no use of secondary or tertiary amines along with Sodium Nitrite in ..... ROS of Cefpodoxime Proxetil.** Nitrosamines impurity (mainly NDMA or NDEA) can only be formed when sodium nitrite reacts with secondary or tertiary amines. **Sodium Nitrite is an inorganic compound and highly soluble in water, methanol and liquid ammonia**. Sodium nitrite has been only used as in side chain MAEM preparation (**Scheme-2**), which is a KSM and ……..is procuring it from the vendor. In vendor manufacturing process, sodium nitrite is used in very first stage to prepare ethyl 2-(hydroxyimino)-3-oxobutanoate from ethylacetoacetate. No secondary or tertiary amine is used in this stage along with sodium nitrite. In this step (Stage-1), sodium nitrite is removing as its sodium sulfate salt through aqueous mother liquid (ML). In further stages, methanol and water are used in the process for extraction and isolation of material, which will remove any traces of sodium nitrite if present. As discussed above, sodium nitrite is highly soluble in water and methanol, therefore, any trace of sodium nitrite will be completely removed during multiple extractions, washings and isolation. Vendor manufacturing process of MAEM is itself capable of removing any traces of sodium nitrite. Therefore, possibility of presence of trace of sodium nitrite as such or in its any reactive form is completely ruled out.

  Whereas, triethylamine is used at last step (Stage-6) as base during preparation of MAEM. Generation of secondary amine impurity (diethyl amine) *via*. degradation of triethylamine is very complex process and it requires aqueous acidic medium. Also, diethyl amine further requires nitrosating source (sodium nitrite or nitrosonium ion) for the generation of nitrosamines impurity (specifically NDEA impurity). But, in Vendor manufacturing process of MAEM, sodium nitrite or any nitrosating source has not been used along with secondary or tertiary amines. Moreover, sodium nitrite is removed as its sodium sulfate salt through aqueous mother liquid (ML) in first stage only which *diminishes the presence of any traces of sodium nitrite in the*

successive stages of MAEM. Therefore, formation of nitrosamines impurity *via.* degradation of triethylamine is ruled out.

In ..... Manufacturing process of Cefpodoxime Proxetil (**Scheme-3**), triethylamine is used in preparation of Cefpodoxime acid (crude) from 7-AMCA (Stage-2). Further, *N*,*N*-dimethylacetamide is used in the purification of crude Cefpodoxime acid to pure Cefpodoximeacid (Stage-3). 1,1,3,3-Tetramethylguanidine (TMG) and *N*,*N*-dimethylacetamide are utilized for the preparation of crude Cefpodoxime Proxetil (Stage-4) from pure Cefpodoxime acid. In **scheme-3**, triethylamine or 1,1,3,3-Tetramethylguanidine (TMG) and *N*,*N*-dimethylacetamide are used as a base and a solvent respectively wherein neither sodium nitrite nor any other nitrosating agent are utilized in the reaction steps. Also, ... manufacturing process of Cefpodoxime Proxetil from 7-ACA comprises of multiple stage extraction, washings and isolation which further ensure that, if any degradation impurity present will be completely removed during the process.

- **Risk evaluation:** There is no possibility of *N*-Nitrosamine impurity (NDMA &NDEA) formation in either synthetic route of API preparation or its side chain MAEM.

Step-3: Risk control

Synthetic route of Cefpodoxime Proxetil is simple, non-hazardous and capable to control all the known and unknown impurities well in their prescribed limits. ……is not using any secondary or tertiary amines along with sodium nitrite, which could be responsible for the generation of N-nitrosamine impurity (NDMA &NDEA).

- **Risk reduction:** Not using any secondary or tertiary amines along with sodium nitrite.
- **Risk acceptance:** The possibility of the presence of trace amount of sodium nitrite is also ruled out, as during MAEM preparation, sodium nitrite is converted to sodium sulphate and removed through aqueous mother liquid at very first stage only.

Results and discussion:

……. ROS for Cefpodoxime Proxetil (from 7-ACA) and side chain MAEM (at vendor site) are discussed below;

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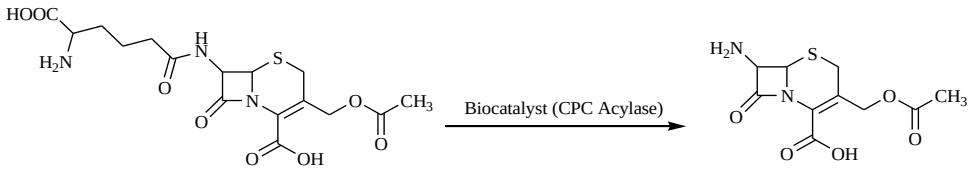
Scheme-1: Preparation of 7-ACA (*at Vendor site*)



Cephalosporin C

7-Aminocephalosporanic acid (7-ACA)

Cephalosporin-C is treated with biocatalyst (CPC acylase) to obtain 7-ACA. The conversion process does not involve use of any secondary or tertiary amines source or nitrosating agent. Therefore, the possibility of the formation of nitrosamine impurity is completely ruled out from synthetic route of 7-ACA.

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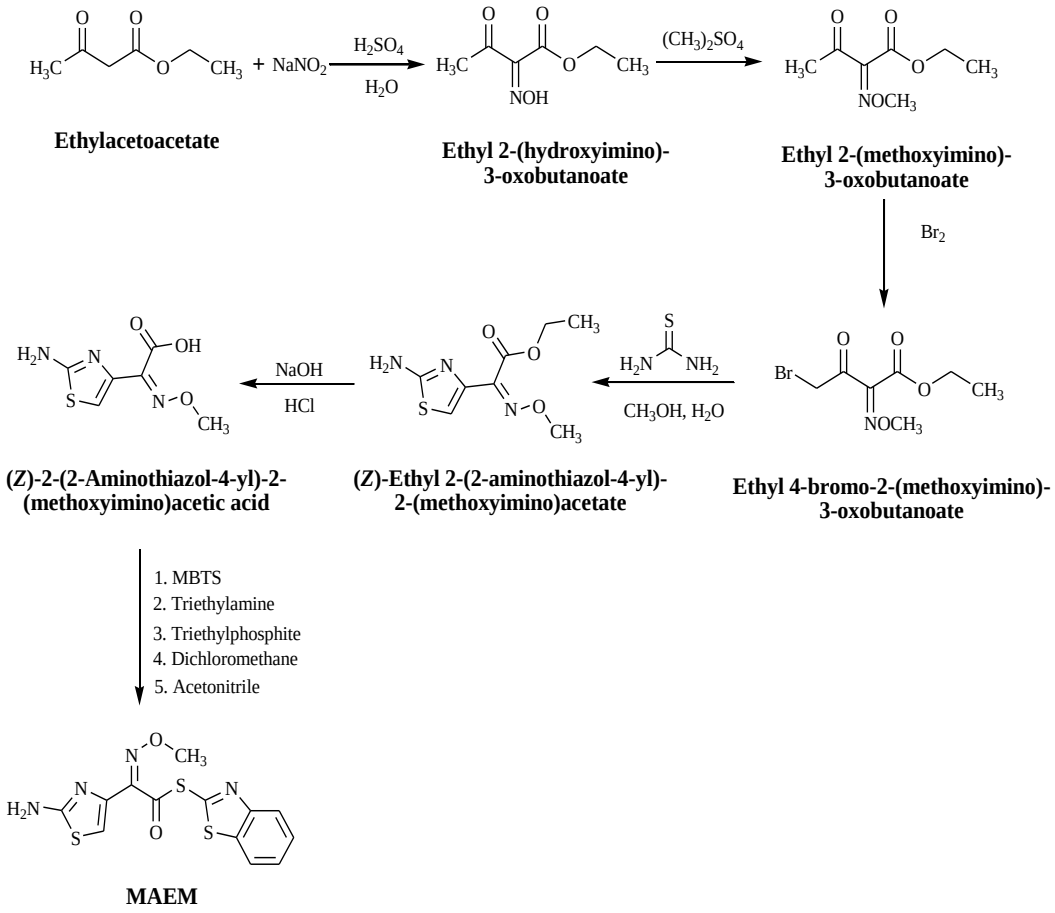
Scheme-2: Preparation of side chain MAEM *(at Vendor site)*



In vendor manufacturing process of MAEM, ethylacetoacetate is converted to ethyl 2-(hydroxyimino)-3-oxobutanoate by using sodium nitrite and sulfuric acid. Ethyl 2-(hydroxyimino)-3-oxobutanoate is further treated with dimethyl sulfate followed by bromination to give bromo intermediate which undergoes cyclization using thiourea followed by basic hydrolysis to give (Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino) acetic acid. This on further treatment with 2-mercaptobenzothiazyl disulfide (MBTS) in presence of triethylamine and triethylphosphite provides MAEM.

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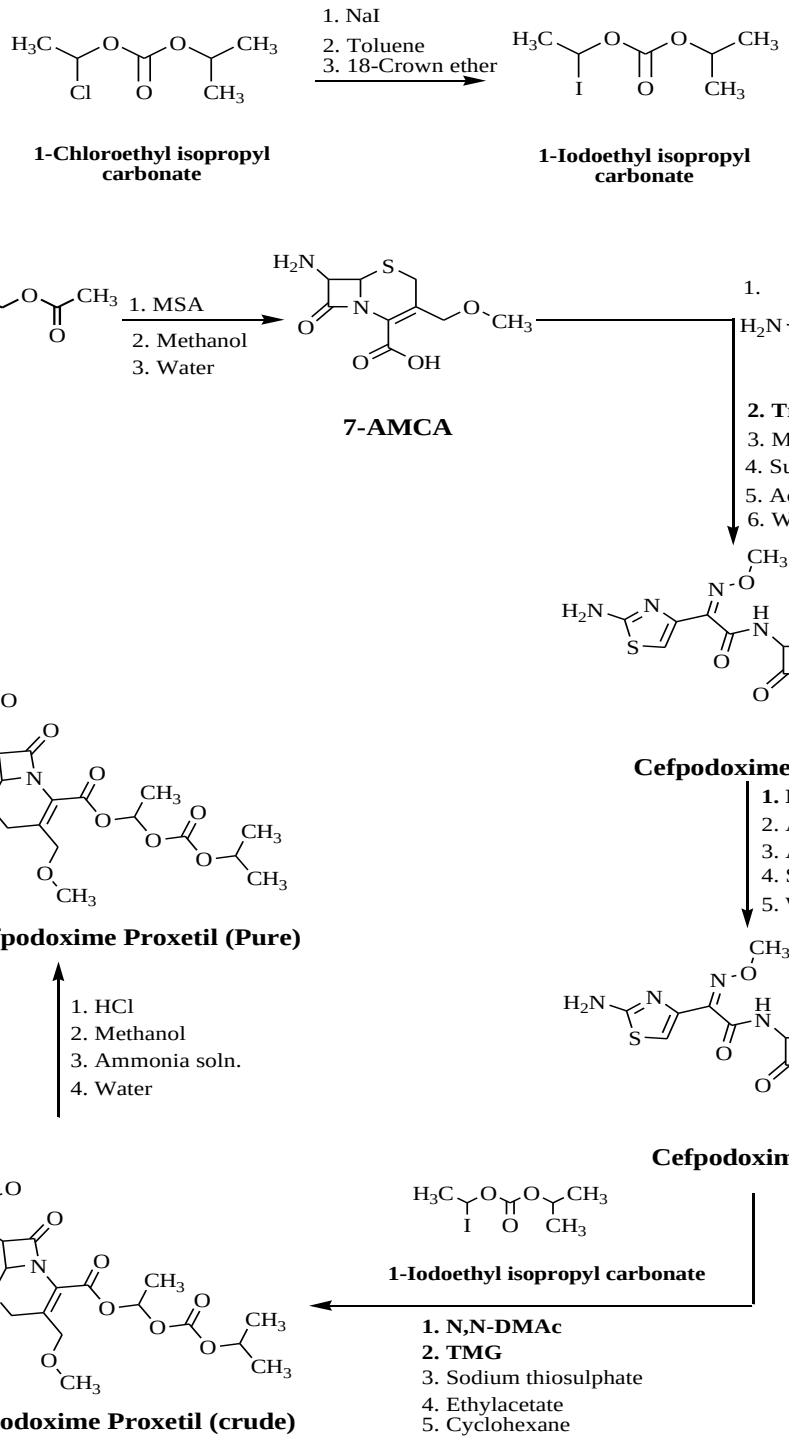

Scheme-3: Preparation of Cefpodoxime Proxetil *(at XYZ. site)*

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At……..7-ACA is first converted to 7-AMCA using MSA in methanol. 7-AMCA is then condensed with MAEM in presence of triethylamine to give Cefpodoxime acid (crude) which is purified by acid-base purification to give Cefpodoxime acid (pure). This Cefpodoxime acid (pure) is further condensed with 1-Iodoethyl isopropyl carbonate in presence of 1,1,3,3-Tetramethylguanidine (TMG) and *N*,*N*-dimethylacetamide to give Cefpodoxime Proxetil (crude) followed by acid-base purification to give Cefpodoxime Proxetil (pure).

In the above discussed synthetic scheme (**Scheme 1, 2 & 3**), this has been further confirmed that, neither vendor nor ..... is using secondary or tertiary amines along with sodium nitrite in its synthetic route for the preparation of 7-ACA, MAEM and Cefpodoxime Proxetil respectively, which may generate N-nitrosamines impurity.

Facility:

We hereby inform that Cefpodoxime Proxetil is manufactured in a dedicated facility. Hence there is no potential for formation of nitrosamine impurities due to cross contamination.

Recovered solvents:

All solvents are recovered in the same manufacturing plant where Cefpodoxime Proxetil is manufactured and no solvent recovered at an outside vendor is used in the manufacturing process/recovered solvent is recovered at a contract facility by the vendor.

We further confirm that neither sodium nitrite nor any amine is used in the recovery of these solvents. Moreover, these solvents are used at the same stage from where these are recovered.

Hence, there is no potential of nitrosamine impurities due to recovered solvents.

Packaging material

As confirmed by the packaging material supplier, packaging materials are free from nitrocellulose or amines.

Hence, there is no potential of nitrosamine impurities due to packaging materials.

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Conclusion:

..... has extensively performed the risk assessment study in Cefpodoxime Proxetil and ruled out any possibility of generation of N-nitrosamine impurity (NDMA &NDEA) in API. Sodium nitrite is an inorganic compound and highly soluble in water, methanol and liquid ammonia. Sodium nitrite has been only used in MAEM preparation **(Scheme-2)**, which is a KSM and ..... is procuring it from the vendor. In vendor manufacturing process, sodium nitrite is used in very first stage to prepare ethyl 2-(hydroxyimino)-3-oxobutanoate from ethylacetoacetate. **No secondary or tertiary amine is used in this stage along with sodium nitrite**. In this step (Stage-1), sodium nitrite is removing as its sodium sulfate salt through aqueous mother liquid (ML). In further stages, methanol and water are used in the process for extraction and isolation of material, which will remove any traces of sodium nitrite if present. As discussed above, sodium nitrite is highly soluble in water and methanol, therefore, any trace of sodium nitrite will be completely removed during multiple extractions, washings and isolation. Vendor manufacturing process of MAEM is itself capable of removing any traces of sodium nitrite. Therefore, possibility of presence of trace of sodium nitrite as such or in its any reactive form is completely ruled out.

Whereas, triethylamine is used at last step (Stage-6) as base during preparation of MAEM. Generation of secondary amine impurity (diethyl amine) *via*.degradation of triethylamine is very complex process and it requires aqueous acidic medium. Also, diethyl amine further requires nitrosating source (sodium nitrite or nitrosonium ion) for the generation of nitrosamines impurity (specifically NDEA impurity). But, in Vendor manufacturing process of MAEM, sodium nitrite or any nitrosating source has not been used along with secondary or tertiary amines. Moreover, sodium nitrite is removed as its sodium sulfate salt through aqueous mother liquid (ML) in first stage only which *diminishes the presence of any traces of sodium nitrite in the successive stages of MAEM*. Therefore, formation of nitrosamines impurity *via*.degradation of triethylamine is ruled out.

In ....., manufacturing process of Cefpodoxime Proxetil (**Scheme-3**), triethylamine is used in preparation of Cefpodoxime acid (crude) from 7-AMCA (Stage-2). Further, *N*,*N*-dimethylacetamide is used in the purification of crude Cefpodoxime acid to pure Cefpodoxime acid (Stage-3). 1,1,3,3-Tetramethylguanidine (TMG) and *N*,*N*-dimethylacetamide are utilized for the preparation of crude Cefpodoxime Proxetil (Stage-4) from pure Cefpodoxime acid. In **scheme-3**, triethylamine or 1,1,3,3-Tetramethyl guanidine (TMG) and *N*,*N*-dimethylacetamide are used as a base and a solvent respectively wherein neither sodium nitrite nor any other nitrosating agent are utilized in the reaction steps. Also ..... manufacturing process of Cefpodoxime Proxetil from 7-ACA comprises of multiple stage

extraction, washings and isolation which further ensure that, if any degradation impurity present will be completely removed during the process. .

Also, no use of secondary or tertiary amines along with sodium nitrite either in vendor manufacturing process of 7-ACA, MAEM or at any stage of manufacturing process of Cefpodoxime Proxetil of ..... Therefore, possibility of generation of nitrosamines impurity are completely ruled out in the overall manufacturing process of Cefpodoxime Proxetil.

..... process for the manufacturing of Cefpodoxime Proxetil is approved from practically all leading global regulatory agencies, in terms of all the Quality Parameters. ..... is committed to produce quality products for human kind in order to alleviate human suffering based on requirements of all stakeholders like patients, doctors, hospitals and health care agencies and institutions.

	Prepared by	**Checked by**	**Approved by**
Signature & Date			
Name			