# A closer look on how to meet the stringent regulatory requirement of genotoxic impurities in Ranolazine

## Introduction

Genotoxic impurities (GTIs) have recently challenged the pharmaceutical industry by virtue of their presence at a level of parts per million (ppm) in drug products, especially in high dosage molecules like Ranolazine, which has a prescribed maximum daily dosage (MDD) of 2000 mg. Regulatory authorities provided guidelines on identification, control, and analytical methods for GTIs[1] reinforcing the need to identify these impurities as well as isolate and analyze them to control their presence in active pharmaceutical ingredients (APIs). There are several approaches[2] that have been reported for the manufacturing of Ranolazine as shown in Figure 1.

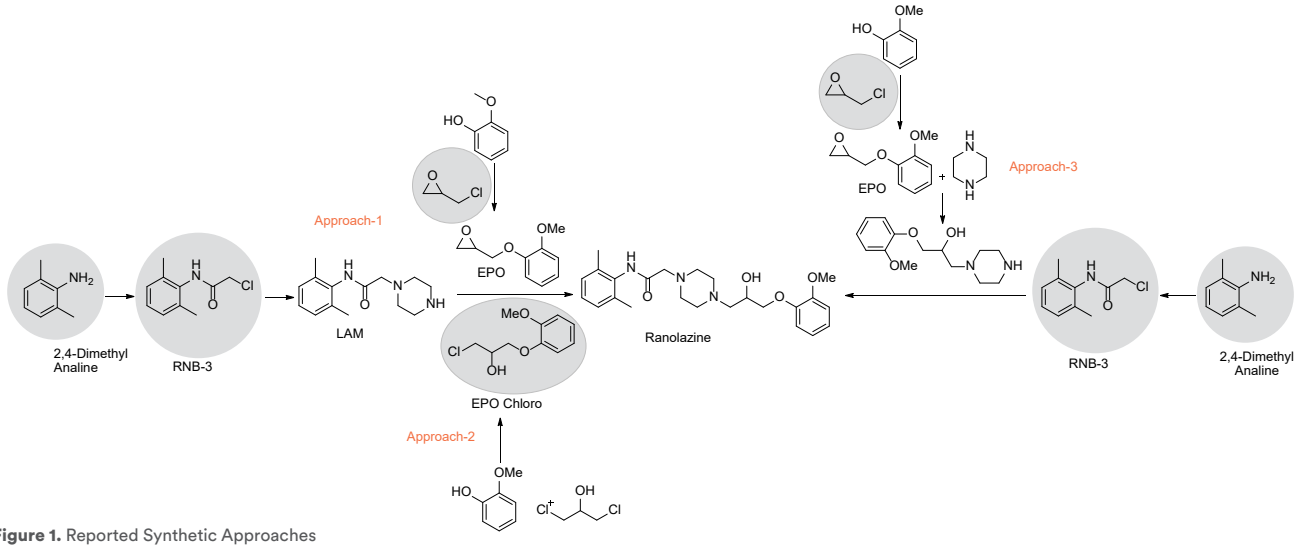
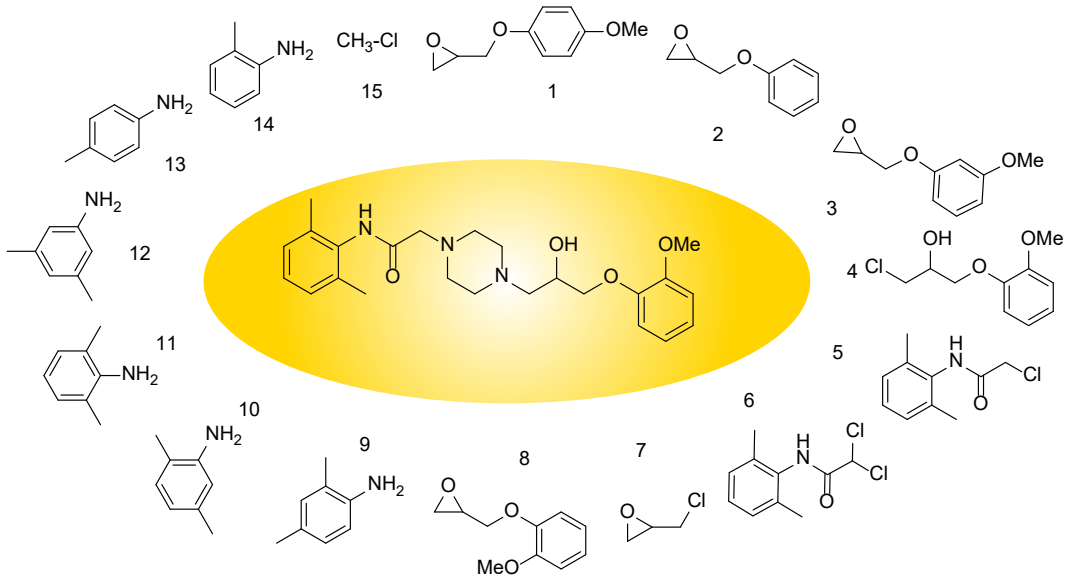



**Figure 1.** Reported Synthetic Approaches

In brief, there are several functionalities such as epoxides, halo derivatives, and aromatic amines that have been identified as structural genotoxic alerts. In all the three approaches described in Figure 1 to synthesize Ranolazine, GTIs/ potential genotoxic impurities (PGIs) are part of the process.

To address the above challenges during the product development phase, the process was designed in such a way that all these PGIs/GTI's are within the control in the manufacturing approach followed by Dr. Reddy's for Ranolazine.



(1) 4-Methoxy EPO
(2) Desmethoxy EPO
(3) 3-Methoxy EPO
(4) EPO Chloro
(5) RNB-3
(6) RNB-3 DCA
(7) Epichlorohydrin
(8) EPO
(9) 2,4-Dimethyl aniline
(10) 2,5-Dimethyl aniline
(11) 2,6-Dimethyl aniline
(12) 3,5-Dimethyl aniline
(13) p-Toluidine
(14) o-Toluidine
(15) Chloromethane

**Figure 2.** Potential Genotoxic impurities during Ranolazine synthesis

## Dr. Reddy's approach to control genotoxic impurities, setting patient centric specifications.

1. At Dr. Reddy's, we have developed robust advanced analytical methods using orthogonal techniques such as HPLC, LC-MS, and GC-MS to detect potential impurities. Acceptable limits have been defined based on threshold of toxicological concern (TTC) approach and compound specific acceptable limits.
2. The level of detection (LOD) and level of quantification (LOQ) of our methods are captured in Table 1 and 2.

**Table 1.** Dr. Reddy's current limit of detection and limit of quantification by LC-MS/GC-MS

| Genotoxic impurity | RNB-3 | RNB-3 DCA | EPO Chloro impurity | 3-Methoxy EPO | 4-Methoxy EPO | Des methoxy EPO | Epichloro hydrin | EPO |
|---|---|---|---|---|---|---|---|---|
| LOD (ppm) | 0.11 | 0.12 | 0.09 | 0.09 | 0.12 | 2.86 | 0.22 | Draft USP method |
| LOQ (ppm) | 0.32 | 0.35 | 0.29 | 0.29 | 0.40 | 9.43 | 0.71 | Draft USP method |

**Table 2.** Dr. Reddy's current limit of detection and limit of quantification by HPLC

| Genotoxic impurity | 2,4-Dimethylaniline | 2,6-Dimethylaniline | 2,5-Dimethylaniline | o-Toluidine | p-Toluidine | 3,5-Dimethylaniline | Chloro methane |
|---|---|---|---|---|---|---|---|
| LOD (ppm) | 1.0 | 2.5 | 4 | 0.08 | 3.3 | 0.15 | 2 |
| LOQ (ppm) | 3.1 | 7.5 | 12 | 0.23 | 10 | 0.45 | 6.3 |

3. We employed a QbD (Quality by Design) approach for process development by considering the stringent limit of genotoxic impurities.
4. We used advanced analytical tools (React IR, Focused beam reflectance measurement for real time particle size analysis etc.) and techniques for process development.
5. Crystallized form of EPO[3] and LAM[4] are used as input materials (critical material attributes) for Ranolazine synthesis to purge out corresponding impurities effectively.
6. Trend data has been generated and process consistency has been established by analyzing several batches (Table 3&4) during the development and it has been confirmed that all 15 impurities are either not detected (ND) or are well below the limit of detection (LoD).

**Table 3.** Genotoxic impurities of 3 batches analysed by using LC-MS/GC-MS

| Impurity Name | 4-Methoxy EPO | Des methoxy EPO | 3-Methoxy EPO | EPO chloro | RNB-3 | RNB-3 DCA | Epichloro hydrine | EPO |
|---|---|---|---|---|---|---|---|---|
| Limit (ppm) | 0.75 | 22 | 0.75 | 0.75 | 0.75 | 0.75 | 1.48 | 0.75 |
| LOQ (ppm) | 0.4 | 9.43 | 0.29 | 0.29 | 0.32 | 0.35 | 0.71 | USP method adopted |
| LOD (ppm) | 0.12 | 2.86 | 0.09 | 0.09 | 0.11 | 0.12 | 0.22 | USP method adopted |
| B#01 | Not Detectable | Not Detectable | Not Detectable | 0.02 | 0.08 | 0.09 | Not Detectable | Not Detectable |
| B#02 | Not Detectable | Not Detectable | Not Detectable | 0.04 | 0.08 | 0.09 | Not Detectable | Not Detectable |
| B#03 | Not Detectable | Not Detectable | Not Detectable | 0.05 | 0.08 | 0.09 | Not Detectable | Not Detectable |

**Table 4.** Genotoxic impurities of 3 batches analysed by using HPLC

| Impurity Name | 2,4-Dimethylaniline | 2,5-Dimethylaniline | 2,6-Dimethylaniline | 3,5-Dimethylaniline | p-Toluidine | o-Toluidine | Chloromethane |
|---|---|---|---|---|---|---|---|
| Limit (ppm) | 6.2 | 76 | 55 | 0.75 | 41.75 | 55 | 680 |
| LOQ (ppm) | 3.1 | 12 | 7.5 | 0.45 | 10 | 0.23 | 6.3 |
| LOD (ppm) | 1 | 4 | 2.5 | 0.15 | 3.3 | 0.08 | 2 |
| B#01 | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | 2 |
| B#02 | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | 2 |
| B#03 | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | Not Detectable | 2 |

## Conclusion

Employing a QbD approach during the process development for Ranolazine API, supplemented by validated highly sensitive orthogonal analytical methods improve both compliance and the control of genotoxic impurities. It could be shown that in case of Ranolazine API, impurities are not detectable or well below the detection level. As a result, this leads to a higher quality of the API, less recalls of the final product for formulators and ultimately contributes to the protection of patient safety.

Dr. Reddy's is well positioned to meet the global demand for Ranolazine API strongly driven by an integrated understanding of API attributes and capacity to manufacture. Dr. Reddy's enables its partners for successful formulation development with different polymorphic variants and a backward integrated manufacturing strategy.

To know more about various offerings and business models, log-into customer service portal XCEED (https://api.drreddys.com/customer_portal/login) or contact us at api@drreddys.com.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## References


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2. US 2013/0090475A1; EP2586774; WO 2006/008753; 2007CH02942; WO 2009153651; WO 2010/025370; US 2009/0318697A1; US 2011/0151258A1; US 2011/0223213; WO 2010/043976; WO 2008/047388; WO 2010/097805; WO 2008/139492, WO 2010/136522.
3. EPO : 1-(2-Methoxyphenoxy)-2,3-epoxy propane
4. LAM :1-[(2,6-Dimethylphenyl)- minocarbonylmethyl]piperazine