

## **INTRODUCTION**

Impurity profiling of drug substances and drug products in the Pharmaceutical industry has become a serious topic in recent years, which can make or break the approval of any pharmaceutical product by the respective regulatory agencies around the world. This approval process of NDA's (New Drug Applications) and ANDA's (Abbreviated New Drug Applications) will allow the Brand and Generic pharmaceutical companies to market the drug products in the corresponding countries in which the approval is being sought for.

The major deficiencies in the DMF's (Drug master files) and ANDA's applications submitted to agencies like USFDA and EMEA, after the review of the application are mainly revolving around the identification, reduction in levels, characterization, justification of levels, and qualification of impurities. This also includes the queries on the data related to the identification of the degradation pathways, illustration of the different degradation pathways, stability studies, validation of stability indicating analytical methods, separation of the identified and unidentified impurities from the drug substance and between the impurities itself, the stress studies under different harsh conditions and the residual solvents and the justifications of their levels

In addition, there is lot of focus on the physical attributes of the drug substance and drug products related to the morphology of the drugs, as in polymorphic forms like crystalline, semi-crystalline or amorphous forms and in the size and shape of the crystals etc. The mixture of multiple polymorphic forms within the single crystallization procedure was observed in several instances and in some other situations the drug converts from one polymorphic form to the pseudo-polymorphic form or another crystal form when stored at different storage conditions or when the drug comes in contact with different excipients and the packaging components. Therefore, the

importance of understanding the distribution pattern and also incorporation of such type of data generated by sophisticated analytical techniques like XRPD (X-Ray Powder Diffraction chromatography), DSC (Differential Scanning calorimeter), Microscopic analysis and Raman Spectroscopy into the drug applications to the governing regulatory bodies is very critical in getting the timely approvals.

Another most important physical property of drug which is severely scrutinized and reviewed and demanded in the drug applications is the particle size data (Analyzed by Malvern analyzer or other equivalent techniques) in cases of solid oral dosage forms, suspensions, inhalation products, transdermal and other topical dosage forms. The extent of distribution of various sizes of the particles in Active Pharmaceutical Ingredients in combination with the polymorphic forms has a huge bearing on the bio-equivalence of the generic drugs when formulated into the above mentioned dosage forms when compared against the brand formulations of the same active ingredient. Also, during the development of the new drugs all the above discussed physical properties play a role in understanding the bio-availability of the proposed NCE (New chemical entity) molecules which are in the pre-clinical, phase I and phase-II studies.

Hence, stringent specifications are being set for various types of impurities and the drug companies need to invest lot of funds and resources very early in the development process to comprehensively understand the impurity profiles, potential degradation pathways, possibility of by-products, interaction studies of the drug substances with various excipients and process aids etc. and also to isolate or synthesize and characterize all the possible impurities and use the impurity standards to develop the analytical methods which subsequently need to be validated as stability indicating methods. In the process of developing the drug products, one has to understand the potential toxicological profiles of each of the identified impurities and its class either being genotoxic,

mutagenic or in cases of organic volatile impurities (OVI) / residual solvents whether they are in the class I, class II or class III.

Having a thorough understanding of the impurity profiles of any drug substance and drug product helps immensely in understanding the safety and efficacy of the drug substances and also helps the pharmaceutical companies to get the approvals without any delay. Getting the approval of ANDA's in right time is very critical in this hyper competitive world of generic landscape in order for the drug companies to compete with their peers. Also, in cases of P-IV applications, the six month market exclusivity in USA will be a big factor to determine the success of the drug products commercially, hence providing the data with full details of the impurity profiling will go a long way in securing the drug approval in any country. On the other side if the impurity profiling and the degradation pathways are not understood well and if the application lacks sufficient data on these topics it will lead to a lengthy review process by way of deficiencies, eventually leading to the competitor company winning the race thereby leading to the huge financial impact on the drug companies.

The literature is replete with several review articles and published papers on the importance of the impurity profiling and degradation pathways for the drug products. Also there is lot of data in the form of publications on the old drugs with respect to the impurity profiling. [References 1 to 10]

However, there are so many recent drug products which are approved by the state governing bodies of various countries in the form of NDA's in the last couple of decades. There is very limited literature and publications on these drugs with respect to impurity profiles and degradation pathways as it is limited to only the innovator companies work on the NCE during the developing phase and is in the confidential data submitted to the regulatory agencies. Still the drug products might not have been studied to the fullest extent in order to understand the complete spectrum of

the degradation possibilities which leaves lot of scope for research. Another factor which becomes important in order to study the impurity profiles and degradation pathways for the recent drugs is that when the drug substance becomes off-patent and is available for the rest of the world to make the generic products of the same drug, each company can synthesize the drug substance in several different ways, which might lead to new impurity profiles.

Hence, there is a strong need for conducting research in this area to systematically study the impurity profiles of the recently approved drugs as there are new inventions in the sophisticated analytical equipments which are enabling to improve the level of understanding of the impurity profiles constantly which might not be at the innovator company's disposal during the development phase. The present research is focused on impurity profiling and exploration of degradation pathways in certain newly approved drugs and their pharmaceutical formulations.