Chapter 7
Development of Stability Indicating Methods

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Abstract The evaluation of the chemical stability studies of small molecule pharmaceuticals rely primarily on the availability of a chromatographic or other separation assay capable of separating and quantifying major impurities and degradation products. A staged approach to the development of stability-indicating HPLC methods, consistent with current regulatory guidelines, is outlined. Practical recommendations are provided for developing forced degradation protocols at every stage of drug development and avoiding common pitfalls that may confuse data interpretation. Consideration is given to special cases such as stereoisomeric drugs, polymorphs, and combination drug products.

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7.1 Introduction

The quality of analytical data generated on stability samples is essential to the successful completion of stability studies and to the ability to draw appropriate conclusions regarding the stability of the product under test [1]. Since the purpose of stability studies is to monitor possible changes to a product or material over time and at different storage conditions, it is expected that all analytical methods applied in the study should be stability-indicating and that only those methods that are truly stability-indicating should be used. Using this broad definition, any method from an X-ray powder diffraction (XRPD) method used to monitor changes of crystalline form to a dissolution method used to evaluate changes in the release rate may be considered stability-indicating if it is demonstrated that it can reliably detect a specific physico-chemical change of the product/material in question. However, for traditional pharmaceutical products, it has become commonplace to reserve the term stability-indicating to describe the method (generally a chromatographic method) used to detect chemical degradation of a drug substance or drug product. This is also the viewpoint taken in writing this chapter. It must be noted here that this is not the case for biologics. International Conference on Harmonisation (ICH) guideline Q5C [2] clearly states that not just one method is stability-indicating but that stability can only be inferred by a combination of analytical methods looking at the identity, purity, and potency (or biological activity) of the drug.

A major challenge in developing a stability-indicating method (SIM) is the access to suitable degraded samples to aid in method development. In an ideal world, these degraded samples would be real-time stability samples that contain all relevant degradants and only those degradants which form under normal storage conditions. Obviously, this is unrealistic for several reasons: development timeline, and how stability is affected by batch characteristics such as process parameters, quality of excipients, and environmental factors such as humidity or temperature. This is why pharmaceutical chemists have to rely on forced degradation samples to develop SIMs. The ability of forced degradation studies (also called stress studies) to forecast real-time degradation has been the object of several studies and is discussed in this chapter.

Formal stability assessment of pharmaceuticals is typically done at three distinct times during development and commercialization: during development, to support the safety and efficacy claims of investigational new drugs; at registration, to ascertain the quality and shelf-life of the marketed product and its ingredients; and finally during the commercialization phase, to ensure the quality of the production and to support site or other changes to the product. Stability information on both drug substance and drug products is required as part of the registration dossier and serves to assign/confirm the shelf-life, determine appropriate storage conditions, define supply chain management, and assure that the quality of the product is unchanged from the time of manufacture to the time of administration to the patient. The approach to SIM development described in this chapter is most suitable for reg-