Hence, when adding an additional source or contemplating the replacement of one source of active raw material with another, all necessary precautions must be taken to ensure interchangeability and this holds true for key excipients as well.

Formulation Development

Formulation development should only commence once the following issues have been suitably addressed:

1. Relevant patents have been accessed and investigated.
2. The appropriate literature search has been undertaken.
3. Regulatory and formulation strategies have been established.
4. The desired API(s) has been ordered and received.

A beneficial approach to formulation development is to critically evaluate and, where possible, to characterize the innovator product with respect to composition, type of granulation (wet granulation or direct compression), and any other qualitative and/or quantitative analyses, which may be practical or feasible. Additional useful information relating to the innovator product may be gleaned by measuring in vitro drug release over a range of pHs and rotational speeds used in dissolution testing as well as inspection of brand labeling for stability information. Conventional microscopy and visual observation may well provide useful information regarding the granulation method used, although caution should be exercised because the results may prove inconclusive and possibly erroneous.

A simple and very useful approach is to determine the pH of the innovator drug product dispersed in a small volume of pH-adjusted purified water and then to compare the result with that yielded by a similar dispersion of the trial formulation. This approach is based on the premise that if the two dispersions provide comparable pH values, the excipient compositions of both innovator and generic formulations are probably similar. Once again, circumspection is necessary because this simple test may sometimes not be sufficiently discriminatory.

Initial trials should be undertaken employing the identical excipients referenced in texts, such as the *Physicians' Desk Reference* [41], *Compendium of Pharmaceuticals and Specialties (Canada)* [42], *Le Dictionnaire VIDAL* [43], and the *Repertorio Farmaceutico Italiano* [44].

Selection of appropriate quantities of key excipients such as binders, disintegrants/dissolution enhancers, compressibility aids, glidants, lubricants, antiadherents, and surface-active agents is an important consideration for the formulation scientist. In this regard, a valuable reference that should be consulted is *The Handbook of Pharmaceutical Excipients* [45].

It would be reasonable to presume that provided the same excipients, as outlined in referenced texts, are used, possible instability/incompatibility issues may be circumvented. However, should it be deemed necessary to use an excipient(s) not present in the innovator product, it will be prudent to evaluate such an excipient(s) for compatibility with the active ingredient using techniques such as a stability indicating HPLC assay, thin-layer chromatography, and/or differential scanning calorimetry [46,47].