APPENDIX 4.A2: DESCRIPTION OF THE FORMULATION-DEVELOPMENT AND SUBSEQUENT EXHIBIT-BATCH MANUFACTURE OF A GENERIC SOLID ORAL DOSAGE FORM (TABLET)

Acquisition of API and Technical Package Following Comprehensive Literature and Patent Reviews

A full set of all specified impurities together with a characterized working reference standard and a list of residual solvents must be included with the Technical Package (which is also known as the Open DMF).

Preformulation Studies on the API

a. Appearance and color (e.g., a white crystalline powder)
b. Polymorphism differential scanning calorimetry/differential thermal analysis (DTA); infrared and x-ray diffraction; tests to confirm identity and, in some cases, the ratio of the desired polymorph-mix
c. Solubility in various solvents including water
d. Particle-size determination

It is advisable to set an in-house particle-size specification, which is then submitted to the supplier describing the method used. A relevant specification can then be set in collaboration with the supplier. A three-tier specification such as those initially adopted by the Canadian TPD and subsequently by various European Regulatory Agencies, FDA, and, more recently, the Australian Therapeutic Goods Administration is recommended.

A typical specification is described hereunder:

$$d(0.9) \leq 60\ \mu m;\ 10\ \mu m \leq d(4.3) \leq 25\ \mu m;\ d(0.1) \geq 2\ \mu m$$

which indicates that 90% of the particles are less than/equal to 60 mm; the "volume mean" lies between 10 and 25 mm, whereas 10% of the particles are greater than/equal to 2 μm. By setting a three-tier specification as outlined, the normal "bell-shaped" distribution curve is implied.

Innovator Product Characterization

a. Qualitative composition refer to all available sources of information (e.g., *Physicians' Desk Reference* and *Compendium of Pharmaceuticals and Specialties* [Canada] from which relevant information can usually be obtained).