Following this, the formulated pharmaceutical product is tested. The product must be stored in exactly the same packaging that will be used for marketing the product. If light exposure causes an unacceptable amount of change in the product, redesign of the packaging is required to increase light protection.

A light dose of 1.2 million lux hours is typically used in photostability studies; this corresponds to an extended period of exposure to indoor light. The light dose received by the samples under test will also depend on the distance from the light source. The light output from the lamps may vary as the lamps age. Frequent measurements of light energy are therefore required at various positions within the light stability cabinet throughout the lifetime of the lamps.

Long-term stability testing

Stress testing, as described above, gives useful information about the likely stability of a formulated product in a relatively short timescale. However, before it can be marketed, a product must undergo long-term stability testing at conditions representing realistic storage conditions. This involves storing the product under predicted worst-case conditions of temperature and humidity in controlled-temperature cabinets or rooms. Samples are removed at intervals and tested over a minimum period of 12 months. The tests performed will include assays of the drug and other formulation components, such as the antimicrobial preservative and determination of drug degradation products. Other tests may be required, such as pH determination, evaluation of the product's physical characteristics and possibly also microbiological tests. Furthermore, specific tests are needed for specific dosage forms.

Any protocol should be designed to ensure that the product remains of adequate quality throughout its proposed shelf-life at the proposed storage conditions when it is marketed.

It is advisable at this stage to perform, in parallel, storage of product at slightly higher than normal temperature/humidity combinations. These are known as accelerated degradation conditions. Reference to accelerated testing in this context should be distinguished from stress testing (discussed above), where more extreme temperatures are used. Accelerated test conditions represent a moderately stressful environment which will allow stability problems to be detected more quickly. Significant degradation at these temperatures gives some early warning of stability problems that are likely to develop on prolonged storage at ambient temperatures.

Climatic zones

The shelf-life of a product depends on its storage temperature and, for susceptible products, also on the humidity. Environmental conditions of temperature and humidity vary between countries around the world. A pharmaceutical manufacturer may market a product in several countries, or indeed continents. In order to avoid having to carry out long-term stability testing under different conditions for each country, and to simplify the long-term stability testing of a product for the global market, four climatic zones have been defined. The world-wide climatic zones recognized by World Health Organization (2009) are mapped in Figure 49.2.

Climatic Zone I. *Temperate climate*, includes Canada, New Zealand, northern Europe, Russia, United Kingdom

Climatic Zone II. *Subtropical and Mediterranean climate*, includes Japan, southern Europe, USA, southern Africa, parts of South America

Climatic Zone III. *Hot and dry climate*, includes Argentina, Australia, Botswana, Middle East, northern Africa

Climatic Zone IV. *Hot and humid climate*, includes Brazil, much of central Africa including Ghana and Nigeria, Indonesia, Nicaragua, the Philippines, Malaysia

These are based on observed temperatures and relative humidities, both outside and inside buildings, from which mean temperatures and average humidity values are calculated. The storage conditions used for long-term stability testing simulate the worst-case average indoor temperature and humidity experienced in that geographical zone (Dietz et al 1993). The values of temperature and humidity set by WHO for long-term stability testing are shown in Table 49.2. Note that for this purpose, WHO has split Climatic Zone IV into two: IVA 'Hot and humid climate' and IVB 'Hot and very humid climate'.

Testing protocols

Because the packaging of a product may affect its stability, products which are undergoing long-term